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Solid-phase synthesis of natural product-like macrocycles by a sequence of Ugi-4CR and S_NAr-based cycloetherification

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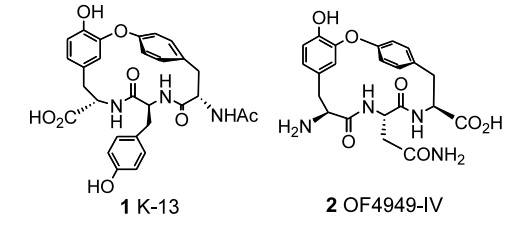
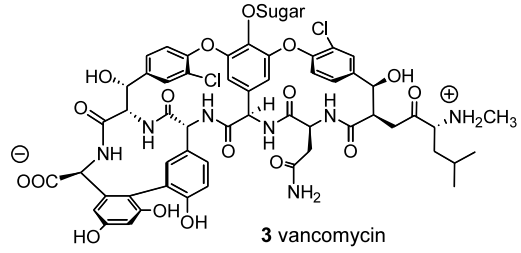
Abstract—An on-resin Ugi four-component reaction followed by an intramolecular nucleophilic aromatic substitution (S_NAr) has been developed for the rapid access to biaryl-ether containing macrocycles.

Many macrocycles with a nonsymmetrical *endo* biaryl ether bridge have been found in Nature. These compounds range from the monocyclic K-13 (**1**),[1] OF-4949 I-IV (**2**) (antifungal),[2] the bicyclic RA series[3] to the structurally complex polycyclic glycopeptide vancomycin (**3**), an important antibiotic used as the last resort for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive bacteria[4] (Fig. 1). Not surprisingly, non-natural biaryl ether containing macrocycles have been designed and compounds with potent bioactivities have been identified.[5]





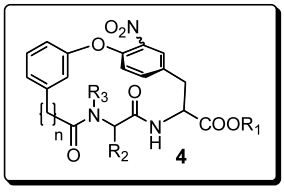


Figure 1.

Interested by the molecular complexity as well as the synthetic challenges posed by vancomycin, a number of new synthetic methodologies have been developed during the past decade that made the construction of the elusive biaryl ether containing macrocycles possible.[4a] In connection with our ongoing project aimed at the development of step-efficient high throughput synthesis of potentially bioactive molecules,[6] we report in this letter a solid-phase synthesis of the biaryl ether containing macrocycles of the generic structure (**4**) by the combined use of Ugi-4CR[7] and S_NAr methodology.[8–10]

Scheme 1 depicts the synthesis of the resin-bound isocyanide (**5**). Hydrolysis of the *N*-formyl α-amino ester (**6**) under standard conditions (K_2CO_3, EtOH, H_2O) followed by esterification with the commercially available Wang resin (loading 0.9 mmol/g) afforded (**8**).[11] Dehydration of the *N*-formyl function ($POCl_3$, Et_3N) provided the supported isocyanide (**5**, loading: 0.74 mmol/g). It is interesting to note that this light yellow resin could be easily prepared in large scale and has a long shelf life without any particular precautions.

With the supported isocyanide (**5**) in hands, its reaction with heptanal (**9a**), butylamine (**10a**), and 3-hydroxy-

Keywords: biaryl ether; macrocycle; multicomponent reaction; S_NAr cycloetherification; solid-phase synthesis; supported isocyanide.
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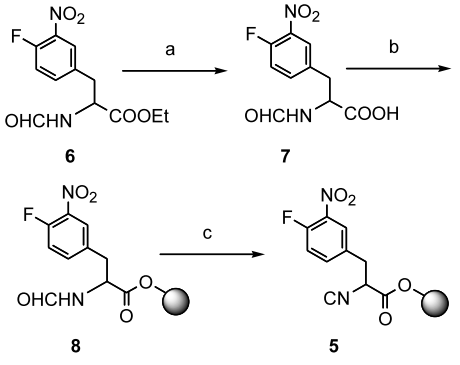
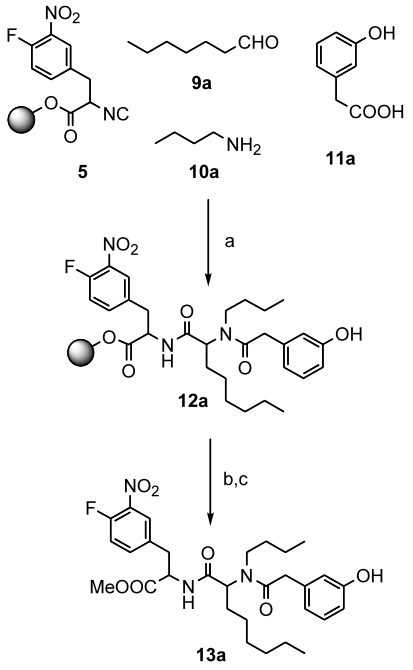
phenylacetic acid (**11a**) was examined (Scheme 2). The efficiency of the on-resin Ugi-4CR was evaluated by quantification of dipeptide ester (**13a**), in turn obtained by resin cleavage (TFA, CH_2Cl_2) and esterification (diazomethane). Following the solution-phase chemistry,[9] the supported Ugi-4CR was first conducted in toluene in the presence of NH_4Cl (entry 1). However, no dipeptide ester **13a** was isolated after resin cleavage and esterification. Therefore, we re-investigated the reaction conditions and the results were summarized in Table 1.[12] Addition of methanol to toluene (entry 2) dissolved all monomeric reagents and the Ugi reaction proceeded to afford dipeptide (**13a**) in 12% yield (calculated for 5 steps starting from the Wang resin). Replacing the toluene by chloroform increased slight the yield of dipeptide (entries 3 and 4). To our delight, using 2,2,2-trifluoroethanol[13] instead of methanol as co-solvent accelerated the reaction rate to afford (**13a**) in a very good overall yield (38%, entry 5). The higher acidity of TFE may be responsible for the improved reaction outcome. The ratio of chloroform to TFE (3/1) seems to be an important factor because an increased proportion of chloroform has an adverse effect (entry 6).

Ring closure via the intramolecular S_NAr reaction on solid support has been reported and is known to be very efficient due to a pseudo-dilution effect of the resin.[14] As shown in Scheme 3, the cycloetherification of polymer-supported dipeptide (**12a**) in DMF in the presence of potassium carbonate proceeded smoothly to provide, after resin cleavage and esterification, the desired macrocycle (**4a**) as a mixture of four separable diastereoisomers. The overall yield of this six-step synthesis was 38% starting from the Wang resin. The low solubility of potassium carbonate in DMF prompted us to use a soluble organic base. Gratifyingly, under otherwise identical conditions, the cyclization promoted by DBU (DMF, room temperature, 3 days) furnished the macrocycle (**4**) in 48% overall yield. To our surprise only two diastereoisomers were formed. Thermal equilibrium experiments conducted in DMSO at 160°C indicated that they are two atropomers. Consequently, it is hypothesized that chiral centers of the peptide backbone were epimerized during the DBU promoted cycloetherification leading to the thermodynamically more stable diastereomer.



Scheme 1. *Reagents and conditions*: (a) K_2CO_3, EtOH, H_2O, 83%; (b) Wang wesin, DCC, DMAP, THF; (c) $POCl_3$, Et_3N, CH_2Cl_2.

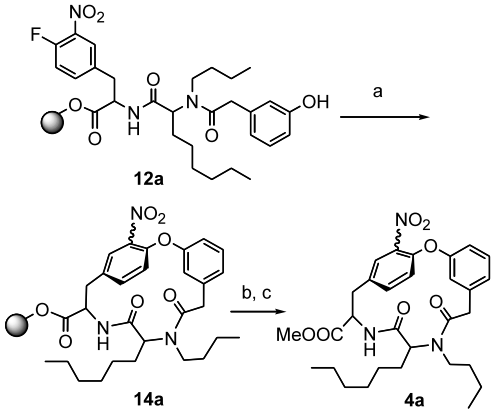


Scheme 2. *Reagents and conditions*: (a) see Table 1; (b) TFA, CH_2Cl_2; (c) CH_2N_2, Et_2O.

Table 1. Survey of conditions for on-resin Ugi-4CR[a]

Entries	Solvent	Yield (%)[b]
1	Toluene/NH_4Cl	N.D.[c]
2	Toluene/MeOH (1/1)[d]	12
3	$CHCl_3$/MeOH (1/1)[d]	15
4	$CHCl_3$/MeOH (3/1)	17
5	$CHCl_3$/TFE[e] (3/1)[f]	38
6	$CHCl_3$/TFE (5/1)	26

[a] The reaction was followed by IR spectrum until the disappearance of isonitrile absorption at 2145 cm^{-1}.
[b] Isolated yield, calculated from the Wang resin.
[c] Not determined.
[d] The reaction was completed after two runs of 48 h.
[e] TFE = 2,2,2-trifluoroethanol.
[f] The reaction was completed after one run of 72 h.



Scheme 3. *Reagents and conditions*: (a) K_2CO_3, DMF (38%) or DBU, DMF (48%); (b) TFA, CH_2Cl_2; (c) CH_2N_2, Et_2O.

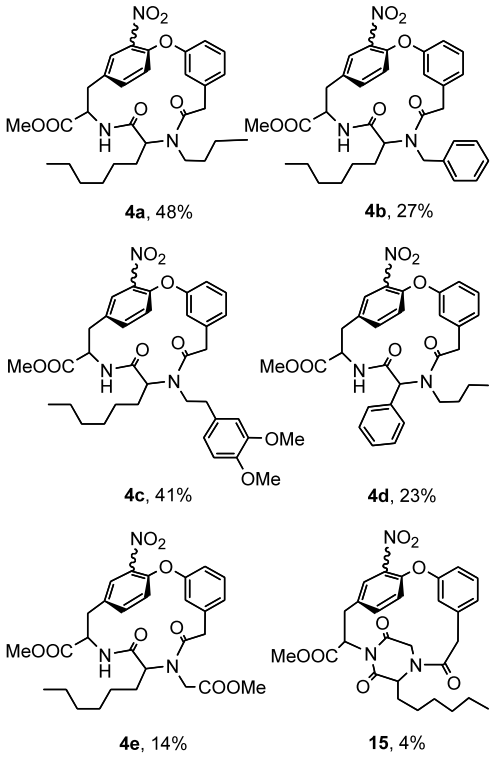


Figure 2.

Figure 2 listed the macrocycles synthesized by a sequence of on-resin Ugi 4CR and intramolecular S_NAr reaction. In all these examples, DBU was used as a base to promote the cyclization and all macrocycles were obtained as two separable atropomers and fully characterized. For macrocycle (**4e**), a diketopiperazine derivative (**15**) was isolated in 4% yield. Although an intramolecular transamidation can account for the formation of (**15**), no experiments have been designed to probe whether the diketopiperazine unit was produced before or after the macrocyclization.

In summary, the on-resin Ugi 4CR/S_NAr cycloetherification sequence reported in this paper allowed the rapid access to a wide range of functionalized biaryl ether containing macrocycles starting from readily available inputs. Our synthesis allowed the introduction of at least four points of diversity and generated significant molecular complexity in an operationally simple two-step sequence. The development of chemistry amenable to the introduction of multiple diversities while still creating molecules of drug-like properties in minimum steps remained a challenging task to synthetic chemists. The combination of multicomponent reaction with other highly efficient transformation, especially cyclization methodologies, has been demonstrated to be one of the highly promising solutions to the problem.[15,16] Further application of MCR/S_NAr cycloetherification sequence to the synthesis of other natural product-like compound libraries is in progress and will be reported in due course.

Acknowledgements

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