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A Rapid Access to Biaryl Ether Containing Macrocycles by Pairwise Use of Ugi 4CR and Intramolecular S_NAr-Based Cycloetherification

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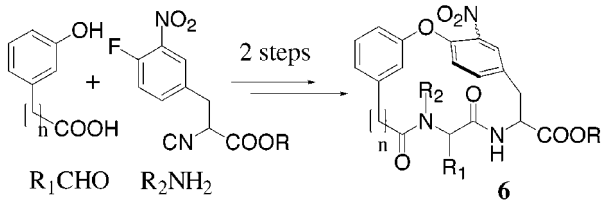
ABSTRACT



From readily accessible starting materials, macrocycles with an *endo* aryl–aryl ether bond are synthesized in only two operations by combination of the Ugi four-component reaction and an intramolecular S_NAr reaction. The nitro group serves as an activator for the macrocyclization and provides a handle for the introduction of functional group diversity. A Ugi reaction promoted by ammonium chloride in aprotic solvent is documented for the first time.

Macrocycles with an *endo* aryl−aryl ether bond have been found in a number of biologically and medicinally important natural products, such as vancomycin family glycopeptides (antibiotics),[1] RA series (antitumors),[2] K-13 (ACE inhibitor),[3] piperazinomycine,[4] and emestrine[5] (both antifungals). Mainly intrigued by the molecular complexity as well as the synthetic challenges posed by vancomycin,[6] a number of new synthetic methodologies have been developed during the past decade that made the construction of illusive biaryl ether containing macrocycles possible.[7,8] The development of efficient synthetic technologies in conjunction with the emergency of high throughput screening of drug candidates have, on the other hand, provided opportunities for the production of libraries of biaryl ether containing macrocycles, inaccessible just a few years back.[9]

A stepwise construction of the peptide backbone incorporating suitably functionalized side chains followed by an intramolecular S_NAr reaction[10] is the main strategy developed

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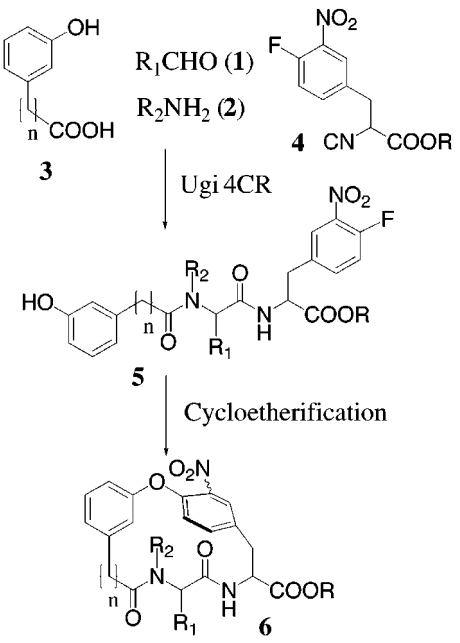
for the production of the biaryl ether containing macrocycles.[11,12] In connection with our ongoing project aimed at the development of step-efficient high throughtput synthesis of bioactive molecules,[13] we envisaged access to the macrocycles of generic structure **6** via a combined use of the Ugi four-component reaction (Ugi 4CR)[14,15] and intramolecular S_NAr-based cycloetherification. The underlying principle is shown in the Scheme 1. Thus, the Ugi reaction

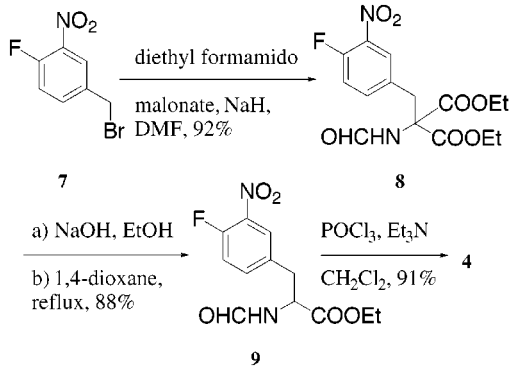
Scheme 1. Two-Step Synthesis of Biaryl Ether Containing Macrocycles



of an aldehyde (**1**), an amine (**2**), a ω-(3′-hydroxyphenyl)-alkanecarboxylic acid (**3**), and an isonitrile (**4**) should give the dipeptide amides (**5**) which, under our previously established conditions, should cyclize to provide the desired *m*,*p*-cyclophanes (**6**). A recent communication from Tempest and Hulme's group[16] employing a similar strategy for the preparation of heterocycles prompted us to report our own results in this Letter.

The unknown ethyl α-(4′-fluoro-3′-nitro)phenethyl isocyanoacetate (**4a**, R = Et) was synthesized as shown in Scheme 2. Alkylation of commercially available diethyl

Scheme 2



formamidomalonate by 4-fluoro-3-nitrobenzyl bromide[17] under standard conditions (NaH, DMF) provided **8** in 92% yield. Partial saponification to the malonate mono ester followed by heating in 1,4-dioxane[18] gave the *N*-formyl α-amino ester (**9**) which was dehydrated ($POCl_3$, Et_3N)[19] to the desired isonitrile (**4a**) in good overall yield.

With the isonitrile in hand, the Ugi 4CR was first examined.[20] At the outset, we were unaware of the compatibility of an amine and a fluoronitro aromatic under Ugi's conditions. Indeed, amines and to a lesser extent alcohols, which are the solvent of choice for the Ugi 4CR, are known to be good nucleophiles for the intermolecular S_NAr reaction.[21] Eventually, stirring a methanol solution of heptanal (**1a**), butylamine (**2a**), 3-hydroxyphenylacetic acid (**3a**), and **4a** did provide the desired dipeptide amide (**5a**), but the yield was only moderate (34%).[22] Therefore, the reaction conditions were reexamined by varying the solvent, temperature, and additives (Table 1). As shown in the table, the reaction did not occur in DMF but proceeded smoothly in trifluoroethanol to provide dipeptide **5a** in 71% yield (entry 4).[23] To

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Table 1. Survey of Conditions for Ugi 4CR[a]

entries	solvent	*T*, °C	additive	yield, %[b]
1	MeOH	rt[c]	none	34[d]
2	MeOH	60	none	16[e]
3	DMF[f]	rt	none	0
4	CF_3CH_2OH	rt	none	71
5	benzene	reflux[g]	none	76
6	toluene	60	none	50
7	toluene	60	NH_4Cl	60
8	toluene	rt	NH_4Cl	33[h]
9	toluene	60	LiBr	35
10	THF[f]	60	NH_4Cl	39

[a] 2.2 equiv each of amine, aldehyde, and acid relative to isonitrile was used. [b] Total yield of two diastereomers in a 1/1 ratio. [c] Room temperature. [d] 83% conversion of **4a** after 24 h. [e] Isonitrile was consumed rapidly, leading to a complex reaction mixture. [f] DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofurane. [g] With Dean−Stark. [h] 63% conversion of **4a** after 48 h.

our surprise, benzene and toluene have also been found to be good reaction mediums for this four-component condensation. Since aprotic solvents are generally considered to be an inappropriate solvent for the Ugi 4CR, a more detailed investigation was carried out.[24] The reaction in toluene at room temperature proceeded slowly and was incomplete after 48 h probably due to the poor solubility of the acid input (entry 8). While lithium bromide (LiBr) had an adverse effect (entry 9),[25] addition of ammonium chloride (NH_4Cl, entry 7) is, on the other hand, beneficial to the reaction. Two points deserved further comments. First, the α-acyloxy amide resulting from the potentially competitive Passerini reaction was not isolated although it is known that nonpolar solvents favor the latter reaction. Second, ammonium chloride, a potential donor of NH_3,[26] did not participate in the Ugi reaction. To the best of our knowledge, this is the first example wherein a Ugi reaction was performed in a nonpolar solvent such as toluene in the presence of ammonium chloride.[27]

Table 2 lists some representative compounds synthesized from five amines, five aldehydes, two acids, and two

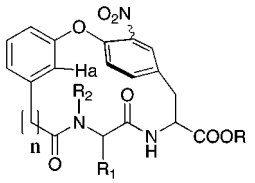
Table 2. Representative Examples of Ugi Products **5**

	R	R_1	R_2	*n*	yield, %
5a	Et	*n*-C_6H_{13}	*n*-C_4H_9	1	60
5b	Et	Ph	*p*-MeO-Ph	1	65
5c	Me	Ph	benzyl	1	73
5d	Me	C_2H_4NHBoc	*n*-C_4H_9	1	43
5e	Me	Ph	benzyl	2	55
5f	Me	phenethyl	*i*-Pr	2	61[a]
5g	Me	*i*-Pr	3,4-dimethoxyphenethyl	2	71

[a] A few drops of methanol were added to help dissolve the starting materials.

isonitriles inputs.[28] In all case, the dipeptide amide was obtained as a mixture of two diastereomers in a ratio of 1/1, separable by preparative TLC on silica gel.

Cycloetherification of the dipeptide amide (**5**) went smoothly in DMF using potassium carbonate as base.[10] Results are summarized in Figure 1. As shown, both 16-



6a n = 1, R = Et, R_1 = *n*-C_6H_{13}, R_2 = *n*-C_4H_9, y: 79%
6b n = 1, R = Et, R_1 = Ph, R_2 = *p*-methoxy Ph, y: 65%
6c n = 1, R = Me, R_1 = Ph, R_2 = benzyl, y: 80%
6d n = 1, R = Me, R_1 = $BocNHC_2H_4$, R_2 = *n*-C_4H_9, y: 72%
6e n = 2, R = Me, R_1 = Ph, R_2 = benzyl, y: 90%
6f n = 2, R = Me, R_1 = Phenethyl, R_2 = *i*-Pr, y: 60%
6g n = 2, R = Me, R_1 = *i*-Pr, R_2 = 3,4-dimethoxy phenethyl, y: 97%

Figure 1.

and 17-membered macrocycles were produced in good yield regardless the substitution patterns. Except for **6g**, two atropisomers were generally formed from a diastereomerically pure dipeptide amide due to the creation of a planar chirality around the biaryl ether linkage. Apparently, the presence of an endocyclic tertiary amide (R_2 residue) did not have a significant influence on the atropostereoselectivity.[29] In most of the cases, the purity of the crude material after conventional workup is higher than 75% according to ^{1}H NMR spectrum, and the two atropisomers are readily separable by preparative TLC. The upfield shift of the proton Ha is characteristic of the cyclic structure and can be used for NMR quantification.

While the nitro function served as an efficient activating group for the key macrocyclization, from the viewpoint of library diversity, its presence provided an extra handle for the introduction of functional group diversity. Some representative high yield transformations are shown in Scheme

(24) Since refluxing using Dean−Stark apparatus is inconvenient from the perspective view of parallel synthesis, only toluene was investigated further.

(25) Positive effect of LiBr in a three-component synthesis of tetracyclic tetrahydroisoqunoline, see: Gonzalez-Zamora, E.; Fayol, A.; Bois-Choussy, M.; Chiaroni, A.; Zhu, J. *J. Chem. Soc., Chem. Commun*. **2001**, 1684−1685.

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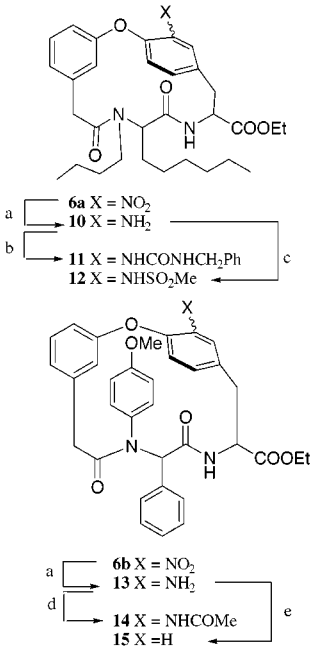
(27) For an earlier study concerning the salt effect on the Ugi reaction, see: McFarland, J. M. *J. Org. Chem.* **1963**, *28*, 2179−2181.

(28) **Typical procedure.** A solution of heptanal (**1a**, 56 μL, 0.42 mmol) and butylamine (**2a**, 40 μL, 0.42 mmol) in dry toluene (1 mL) was stirred at room temperature for 1 h. 3-Hydroxyphenylacetic acid (**3a**, 63.3 mg, 0.42 mmol), isonitrile (4a, 50.3 mg, 0.19 mmol), and NH_4Cl (22.2 mg, 0.42 mmol) were then introduced. After being stirred at 60 °C for 20 h, the reaction mixture was diluted with water and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2, heptane/EtOAc = 60/40) to afford **5a** (67 mg, 60%) as a mixture of two diastereoisomers (1/1 ratio).

(29) For examples of atropselective cycloetherification, see ref 6 and Bois-Choussy, M.; Neuville, L.; Beugelmans, R.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 9309−9322.

Scheme 3[a]



[a] Reagents and conditions: (a) H_2, Pd/C, EtOH, 95-99%; (b) $PhCH_2NCO$, CH_2Cl_2, 73%; (c) MsCl, Et_3N, CH_2Cl_2, 55%; (d) Ac_2O, Et_3N, CH_2Cl_2, 81%; (e) $NaNO_2$, Cu_2O, H_3PO_2, THF−H_2O, 86%.

3. Thus, hydrogenolysis of **6a** under standard conditions (Pd/C, H_2, EtOH) provided the aniline **10** in 99% yield, which was then converted into the corresponding urea (**11**) and methylsulfonamide (**12**) by its reaction with benzyl isocyanate and methansulfonyl chloride, respectively. Similarly, macrocycle **6b** was transformed into the acetamide **14** and de-aminated compound **15** in good yield under standard conditions.

In summary, we have developed a two-step synthesis of biaryl ether containing macrocycles from readily available starting materials. The sequence of transformations gave rise to a marked increase in molecular complexity and allowed for the incorporation of at least three points of diversity. The presence of the nitro group in macrocycles allowed for the easy introduction of functional group diversity into the existing macrocycles, increasing further the molecular diversity. In the course of this study, an ammonium chloride promoted Ugi 4CR in aprotic solvent was documented and should find application in solid-phase synthesis because of the good swelling property of toluene.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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