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Solid Phase Synthesis of Pyrroles Derived from a Four Component Condensation

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Abstract: *The first synthesis of tetra- and penta-substituted pyrroles via a 1,3-dipolar cycloaddition of alkynes to polymer bound münchnones is reported. These münchnones are generated in a single step from a four component condensation product of an aldehyde, an amine, a carboxylic acid and an isocyanide. The process produces pyrroles in good overall yield and high purity.* Copyright © 1996 Elsevier Science Ltd

The popularity of peptide and oligonucleotide combinatorial libraries in drug discovery[1] has inspired the development of chemically tagged,[2] spatially dispersed (SDCL)[3] and most recently radio frequency (RF) encoded small organic molecule combinatorial libraries.[4] When coupled with high-throughput biological screening protocols these methods represent efficient alternatives to traditional medicinal chemistry approaches aimed at lead discovery and optimization.[4] To this end, a variety of solution phase chemical transformations have been reevaluated[5] and applied to single or multistep syntheses on solid support.[6] The 1,3-dipolar cycloaddition of münchnones to a variety of dipolarophiles as a means to generate pyrroles, pyrrolines and imidazoles is well established in solution.[7] Herein we wish to report the first synthesis of tetra- and penta-substituted pyrroles *via* a 1,3-dipolar cycloaddition of alkynes to polymer bound münchnones. The latter having been generated in a single step from an Ugi four component condensation (U-4CC)[8] product.

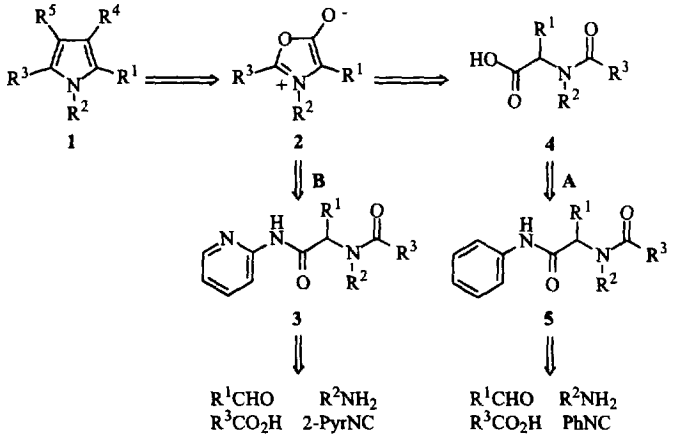

Figure 1. Retrosynthetic analysis of pyrroles **1**.

The retrosynthetic analysis for pyrrole **1** is outlined in Figure 1. The münchnone **2** could be generated in one step from the *N*-acyl-*N*-alkyl-a-amino amide **3** or the *N*-acyl-*N*-alkyl-α-amino acid **4**, itself the hydrolysis product of *N*-acyl-*N*-alkyl-a-amino amide **5**. Both **3** and **5** are prepared in one step *via* an U-4CC of a 1° amine,

an aldehyde, a carboxylic acid and 2-pyridylisocyanide (2-PyrNC) or phenylisocyanide (PhNC)[9] respectively. Given the large number of commercially available reagent inputs, the cycloaddition of the münchnones generated from the U-4CC with alkynes could produce library of up to 10^8 different pyrroles.[10]

Facile hydrolysis of amides **3** and **5** on solid support was critical to the success of our strategy. Unfortunately, 2° amides are difficult to hydrolyze.[11] However other specialized 2° amides such as 2-azidophenylamides[12] and 1-cyclohexenylamides[13] could be converted to their corresponding acids and/or esters. Unfortunately, the need for catalytic hydrogenation during the hydrolysis of 2-azidophenylamides limits the scope of such a method. As an alternative approach a suitable isocyanide which would undergo U-4CCs on solid support in good yield and provide a convertible amide functionality was developed. Specifically, this method would allow direct transformation of the U-4CC solid bound product to the münchnone **2** or the amino acid **4** under mild conditions. Initial experiments showed that the *N*-acyl-*N*-alkyl-α-amino amides prepared using benzyl isocyanide (BnNC) could be converted to the corresponding *N*-acyl-*N*-alkyl-α-amino acids through treatment with *t*-Boc_2O-DMAP in THF followed by 1N LiOH (H_2O-THF) at 23°C.[14] However, both reactions were very slow ($t_{1/2}$>7 days at 23°C) and low yielding overall (10%). The rate of both steps as well as the overall conversion improved drastically when BnNC was replaced with PhNC. Amide **5** was acylated (23°C, 45 min) and hydrolyzed (23°C, 1.5 h) in one pot to yield acid **4** quantitatively.[15]

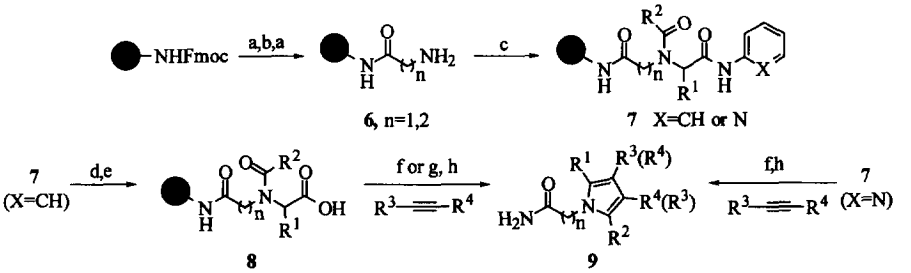

Figure 2. (a) 20% piperidine-DMF, 23°C, 20 min. (b) HBTU, HOBT, N-Fmoc-amino acid (n=1 or 2), DIEA, DMF, 23°C, 4 h. (c) R^1CHO, PhNC or 2-PyrNC, R^2COOH, 1:1:1 $CHCl_3$-Pyridine-MeOH, 65°C, 48 h. (d) TEA, DMAP, Boc_2O, CH_2Cl_2, 23°C, 18 h. (e) 4:1 (1N LiOH-5%H_2O_2)-THF, 23°C, 6 h. (f) acetylene, Ac_2O, 65-100°C, 24-48 h. (g) acetylene, isobutyl chloroformate, TEA, toluene, 100°C, 24-48 h. (h) 20% TFA -CH_2Cl_2, 23°C, 20 min, azeotrope toluene.

The synthetic scheme for the preparation of multi-substituted pyrroles on solid support is shown in Figure 2. This study was focused on amine bearing linkers due to the large number of commercially available bifunctionalized amines (e.g. amino acids, amino alcohols, etc.). Fmoc-Rink resin[16] was deprotected, acylated[17] with the coresponding *N*-Fmoc-amino acid (n=1,2) and deprotected again to yield support bound amine **6** in greater than 90% yield. Subsequent U-4CC with aldehydes, PhNC, and carboxylic acids ($CHCl_3$-MeOH-pyridine 1:1:1, 65°C, 48 h) gave **7** (X=CH, 50-70%). Pyridine was a necessary co-solvent, buffering the reaction mixture and stabilizing the isocyanide. The two step hydrolysis of the phenyl amide **7** (X=CH) to the acid **8** proceeded quantitatively as judged by ^1H NMR analysis of TFA cleavage material. Reaction of **8** and alkynes in either neat Ac_2O or with isobutyl chloroformate-TEA-toluene (65-100°C, 24-48 h) and subsequent cleavage from the solid support (20% TFA-CH_2Cl_2) provided pyrroles **9a-j** in 26-72% overall yield (Table 1). This method produced very high purity pyrroles as recovered from solid support. Figure 3 shows the ^1H NMR spectrum of crude **9j** which was isolated in 40% overall yield after 8 steps. *This testifies to a highly efficient process of yield is consistent with a process in which each synthetic transformation wa achieved with greater than 85% yield per with no chromatographic purification!*

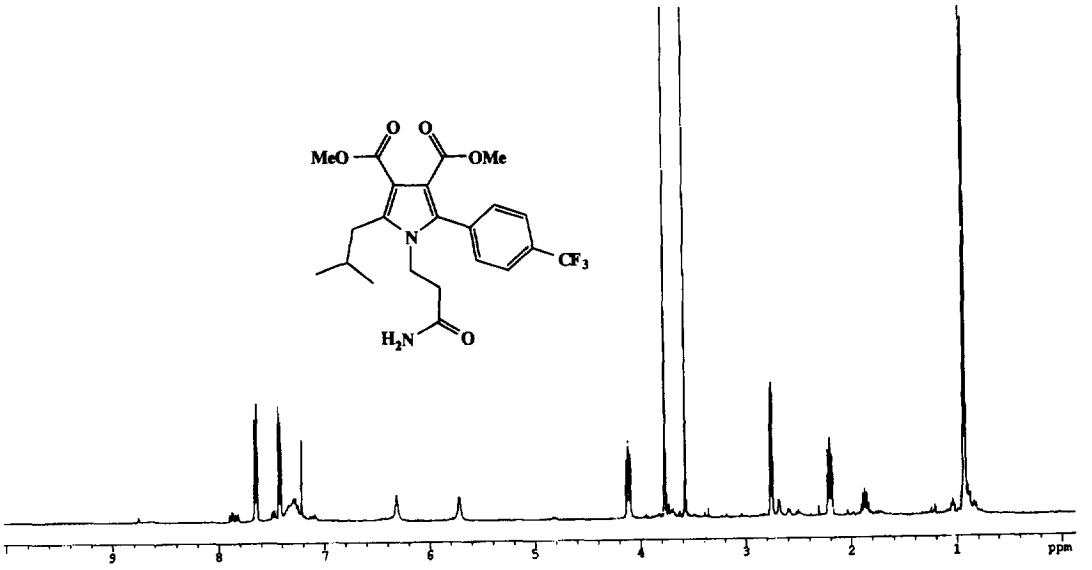

Figure 3. 400 MHz ^{1}H NMR of crude pyrrole **9j** in $CDCl_3$.

Alternatively, by replacing PhNC with 2-PyrNC (Figure 2), the *N*-acyl-*N*-alkyl-α-amino amide **7** (X=N) was cyclized directly to the münchnone **2** (Ac_2O, 100°C), which was trapped *in situ* with a variety of alkynes to yield pyrroles **9b-f** (Table 1). Although method B is slightly lower yielding than method A, it does provide the final product in one step from the U-4CC. The overall yield of this process is being optimized at present.

Table 1. Yields of Pyrroles **9** from Solid Support. [18]

	n	R^1	R^2	R^3	R^4	% Yields[a,b]
9a	1	Et	4-Br-C_6H_4	CO_2Me	CO_2Me	42 (--[c])
9b	2	Et	4-Br-C_6H_4	CO_2Me	CO_2Me	46 (14)
9c	2	Et	4-Br-C_6H_4	CO_2H	CO_2H	49 (14)
9d	2	Et	4-Br-C_6H_4	Et	CO_2Et	35 (6)[d]
9e	2	Et	4-Br-C_6H_4	H	CO_2Et	26 (6)[d]
9f	2	i-Pr	$C_6H_5CH_2$	CO_2Me	CO_2Me	72 (16)
9g	2	n-Pr	Ph	CO_2Me	CO_2Me	46 (--[c])
9h	2	i-Pr	4-MeO-C_6H_4	CO_2Me	CO_2Me	45 (--[c])
9i	2	n-Bu	4-Me-C_6H_4	CO_2Me	CO_2Me	45 (--[c])
9j	2	i-Bu	4-CF_3-C_6H_4	CO_2Me	CO_2Me	40 (--[c])

(a) Overall yields of method A were determined from the mass balance of pure material after chromatography, based on the initial substitution level of the Rink resin. (b) Numbers in paranthesis correspond to the overall yields of method B. (c) No data available. (d) The ratio of regioisomers as determined by ^{1}H NMR of the crude material (80:20 for **9d**; 70:30 for **9e**). The structures of the regioisomers have been assigned based on ^{1}H nOe data.

In conclusion, a novel and highly efficient method for synthesis of tetra and penta-substituted pyrroles from the product of a four component Ugi condensation between an aldehyde, a 1° amine, a carboxylic acid and PhNC or 2-PyrNC has been developed. This method is being applied towards the synthesis of pyrrole based combinatorial libraries. Investigation of tetra substituted NH-pyrrole synthesis and the reaction of the polymer

bound münchnones with additional dipolarophiles, including those leading to new heterocyclic systems are currently underway and will be reported in due course.

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