Solid-Phase Synthesis of Highly Substituted Peptoid 1(2*H*)-Isoquinolinones

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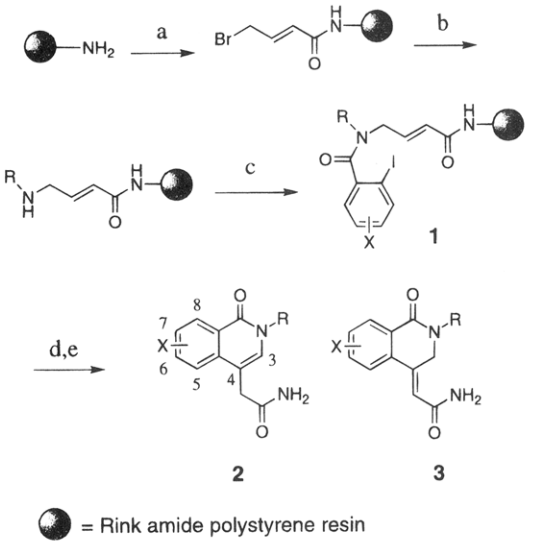
The rapid synthesis of large organic compound collections by combinatorial methods on solid supports is a promising strategy for the discovery of new pharmaceutical leads.[1] We have discovered trimeric N-substituted glycines (peptoids) with nanomolar binding affinities for the α-adrenergic and μ-opiate receptors from such combinatorial libraries.[2] One focus of our drug discovery effort is to increase the structural rigidity, complexity, and diversity of the libraries. This can be done by introducing new monomeric backbone units with greater functionality and by application of powerful solution phase organic reactions to the solid phase. In particular, we wanted to explore homogeneous transition metal-catalyzed reactions. We wish to report here the solid-phase synthesis of highly substituted 1(2*H*)-isoquinolinones bearing peptoid side chains.

The first step in the synthesis is to couple *trans*-4-bromo-2-butenoic acid (bromocrotonic acid)[3] to deprotected Rink amide resin (Scheme 1). Subsequent S_N2 amine displacement under the conditions developed for the submonomer method of peptoid synthesis[4] cleanly gives the unsaturated monopeptoid, with no evidence of competing S_N2' attack at the α-position. Acylation of the monopeptoid with an *o*-iodo carboxylic acid chloride gives an intermediate poised to undergo a palladium(0)-catalyzed intramolecular Heck reaction to the peptoid backbone, which should be facilitated by the electron-withdrawing carboxamide group. The intramolecular Heck reaction is a powerful method for forming five, six, or seven-membered rings fused to aromatic rings and has found numerous recent applications.[5,6] The *o*-iodo or *o*-bromo carboxylic acids can readily be prepared from commercially available anthranilic acids as well as from heterocyles such as pyridine- or pyrazinecarboxylic acids. In the initial experiment resin bound monopeptoid **1a** (R = *i*-Bu) capped with *o*-iodobenzoyl chloride was treated with $Pd(Ph_3P)_4$ in DMA in the presence of NaOAc and Ph_3P for 5 h at 85 °C. A facile cyclization occurred, which was immediately apparent by HPLC of the crude product obtained by treatment of the resin with 95/5 TFA/H_2O. The uncyclized C-terminal amide resulting from cleavage of **1a** elutes as a broad peak at 23.9 min while the cyclized product is a sharp peak with a retention time of 18.7 min (Vydac C-18 analytical column, gradient 0−80% CH_3CN in H_2O with 0.5% TFA over 40 min). The cyclized product was initially assigned structure **3a** in which β-elimination of PdH results in an exocyclic double bond. However, a combination of HMBC/HMQC and ROESY NMR experiments revealed the correct structure to be **2a**. The HMBC spectrum shows a diagnostic three-bond C,H coupling between the one proton vinylic singlet (H-3) at 7.2 ppm and the isobutyl side chain methylene carbon at 56.7 ppm, which is only possible if the double bond is endocyclic. The ROESY spectrum shows cross-peaks between the singlet at 7.2 ppm and both the isobutyl methylene doublet at 3.8 ppm and the 2 proton singlet of the CH_2CONH_2 group at 3.6 ppm, but no cross-peaks with any of the aromatic protons which is also consistent with structure **2a** rather than **3a**.

These conditions were subsequently extended to monopeptoids containing several different amine-derived side chains, as well as different aromatic substitution patterns. The results are shown in Table 1. These reactions were normally performed on 100−150 mg of polystyrene resin (0.05−0.075 mmol), but reactions on a 500 mg scale proceeded equally well. When a substituent was present ortho to the iodo group in **1** a mixture of products **2** and **3** was obtained. For example, cyclization of **1d** gave a mixture of **2d** (t_R = 20.16 min) and **3d** (t_R = 21.33 min) in a ratio of 1/3.2. The ^1H NMR of **2d** was very similar to that of **2a** (H-3 at 7.18 ppm), whereas **3d** showed a corresponding one-proton singlet at 6.2 ppm. The assignment of structure **3d** to the major isomer was

Scheme 1[a]



[a] Key: (a) 0.6 M 4-bromo-2-butenoic acid, 0.6 M DIC in DMF, 2 × 30 min, rt; (b) 2.0 M RNH_2 in DMSO, 2 h, rt; (c) 0.5 M iodo acid chloride, 0.5 M triethylamine, rt, 2 × 30 min; (d) $Pd(Ph_3P)_4$, NaOAc, Ph_3P, DMA, 85 °C, 5 h; (e) 95/5 TFA/H_2O, 20 min, rt, then lyophilize.

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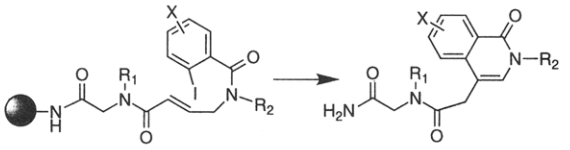
Table 1. Characterization of Various Individual 2-Substituted 1(2*H*)-Isoquinolinones

Entry	Ring A	R	Purity (**2**/**3**)[a]	Yield[b]
2a	H	*i*-Bu	83	69
2b	H	CH_2CH_2Ph	80	65
2c	H	Ph	>70	85
2d	5-Me	*i*-Bu	94 (1/3.2)	92
2e	8-F	*i*-Bu	90	80
2f	6,7-diOMe	*i*-Bu	95	77
2g	7-Cl	*i*-Bu	90	79
2h	5-OMe	*i*-Bu	93 (1.7/1)	69

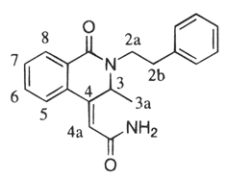
[a] Determined by C-18 HPLC monitored at 214 nm. Values in parentheses are ratios of **2** to **3**, otherwise only **2** was observed. [b] Yield of crude product after lyophilization from acetic acid.

Scheme 2



confirmed by HMBC/HMQC and ROESY. The ROESY experiment was particularly informative as it showed a strong NOE cross-peak between the singlet at 6.2 ppm and the aromatic methyl at 2.5 ppm, which is only possible if the vinylic proton is located on an exocyclic double bond. This also assigns the *Z* double bond geometry. Interestingly, compound **4,** which has a methyl group at C-3, was obtained exclusively as the exocyclic isomer.[7] Finally, when **1a** was cyclized at 60 °C for 18 h rather than 85 °C for 5 h two products having identical MS parent ions ($MH^+ = 259$) were observed at 18.6 min and 19.9 min in a ratio of 2.3/1. Comparison of the ^1H NMR spectra of the two products strongly suggests that the minor product of longer retention time is exocyclic isomer **3a.** Together, these results suggest that the initially formed product of the Heck reaction is isomer **3** and that subsequent readdition of PdH and elimination in the opposite direction gives the thermodynamically more stable isomer **2**. Thus, the effect of the ortho-aromatic substituent or the 3-methyl group could be to hinder readdition of PdH.

In addition to the cases shown in Table 1 we have succesfully extended the Heck reaction sequence by using 2-bromopyridine-3-carboxylic acid to produce **5** under essentially the same reaction conditions. Extensions to other *o*-haloheteroarenecarboxylic acids can readily be imagined.[8] The process works equally well when a dipeptoid is used, producing an isoquinolinone with an extended side chain (Scheme 2). These extended hybrid peptoid/isoquinolinones now have three variable positions, R_1 and R_2 (derived from primary amines) and the aromatic substituents.



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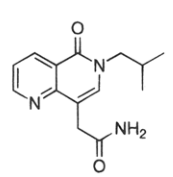

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Since the peptoid portion of the molecule can be rapidly assembled from readily available and highly diverse building blocks by robotic synthesis[9] using the submonomer method, the synthesis of designed libraries containing 10^3–10^4 members should be possible. Since it was considered that the nature of R_2 could have a significant impact on the intramolecular Heck reaction we separately synthesized seven monopeptoids bearing different amine side chains and mixed the resins together to make an equimolar mixture. The resin mixture was then acylated with *o*-iodobenzoyl chloride and cyclized. The HPLC of the crude cleavage mixture is shown in Figure 1. Although it is difficult to quantitate the relative amounts of each product (due to differences in extinction coefficients), the mixture is close to equimolar. The mass spectrum of the crude mixture shows all seven of the expected parents. In addition, the identitites of the seven major peaks in the HPLC chromatogram were established individually by electrospray mass spectrometry. This experiment demonstrates the feasibility of constructing a diverse 1(2*H*)-isoquinolinone library on solid supports based on organotransition metal chemistry.

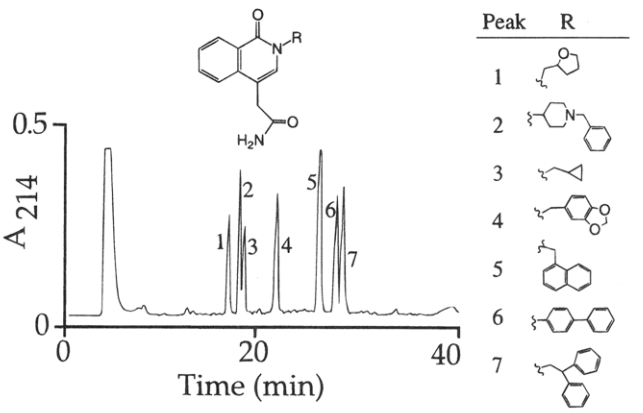

Figure 1. Reversed-phase HPLC chromatogram of a seven-component mixture of 2-substituted 1(2*H*)-isoquinolinones synthesized via an intramolecular Heck reaction on a solid-support. HPLC conditions: Vydac C-18 column (5 μm, 300 Å, 4.6 × 250 mm), linear gradient of 0–80% B in 40 min at a flow rate of 1 mL/min (solvent A = 0.1% TFA in water, solvent B = 0.1% TFA in acetonitrile).

In conclusion, the application of the intramolecular Heck reaction to the solid phase has allowed the creation of a new class of hybrid heterocyclic peptoids. Application to the robotic synthesis of diverse libraries is in progress.

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Supporting Information Available: Experimental details and ^1H NMR, 2D NMR, and high-resolution mass spectrometry data for selected isoquinolinones (17 pages).

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