Solid-Phase Synthesis of Highly Substituted Peptoid 1(2H)-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 dopamine 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(2H)-isoquinolinones bearing peptoid side chains.

The first step in the synthesis is to couple trans-4-bromo-2-butenoic acid (bromocrotonic acid3) to deprotected Rink amide resin (Scheme 1). Subsequent S02 amine displacement under the conditions developed for the submonomer method of peptoid synthesis4 cleanly gives the unsaturated monopeptoid, with no evidence of competing S02 attack at the α-position. Acylation of the monopeptoid with an α-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 α-iodo or α-bromo carboxylic acids readily be prepared from commercially available anthranilic acids as well as from heterocycles such as pyridine- or pyrazinecarboxylic acids.

In the initial experiment resin bound monopeptoid 1a (R = i-Bu) capped with α-iodobenzoyl chloride was treated with Pd(PPh3)4 in DMA in the presence of NaOAc and Ph3P 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/H2O. 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% CH3CN in H2O with 0.5% TFA over 40 min). The cyclized product was initially assigned structure 3a in which β-elimination of Ph3P 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 CH2CONHz 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 (0.5−0.75 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 (f2 = 20.16 min) and 3d (f3 = 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

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 vinlyc 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. 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 successfully 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. 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, R1 and R2 derived from primary amines) and the aromatic substituents.

Since the peptoid portion of the molecule can be rapidly assembled from readily available and highly diverse building blocks by robotic synthesis using the submonomer method, the synthesis of designed libraries con-