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Solid Phase Synthesis of Spiroindoline

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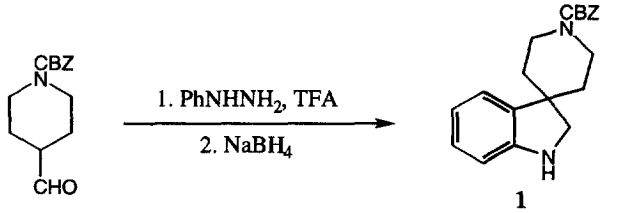
Abstract: A method for solid phase synthesis of spiroindolines using the Fischer indole reaction is described. Various arylhydrazines react cleanly with polymer bound piperidine-4-carboxaldehyde in TFA/CH_2Cl_2. The products are isolated in good yields and high purity.

While solid phase synthesis has been extensively used for generating molecular diversity in oligomers and small organic molecules,[1] it is still a major challenge to construct structurally defined target molecules on solid support. We have been interested in constructing combinatorial libraries containing heterocyclic molecules as a core structure. The spiroindoline nucleus is an important pharmacophore capable of interacting with diverse receptors.[2] Thus, it is an attractive target for library generation. Herein we report the facile synthesis of spiroindoline derivatives using the Fischer indole reaction[3] on solid support.

The synthesis of spiroindoline **1** has been studied in solution using the Fischer indole reaction.[4] The reaction was not successful with classical Fischer indole catalysts such as Lewis acids and mineral acids. However, the reaction gave clean product in high yield when TFA was used as a catalyst (Scheme 1). We anticipated that this method would be a good starting point for solid phase spiroindoline synthesis.

Scheme 1



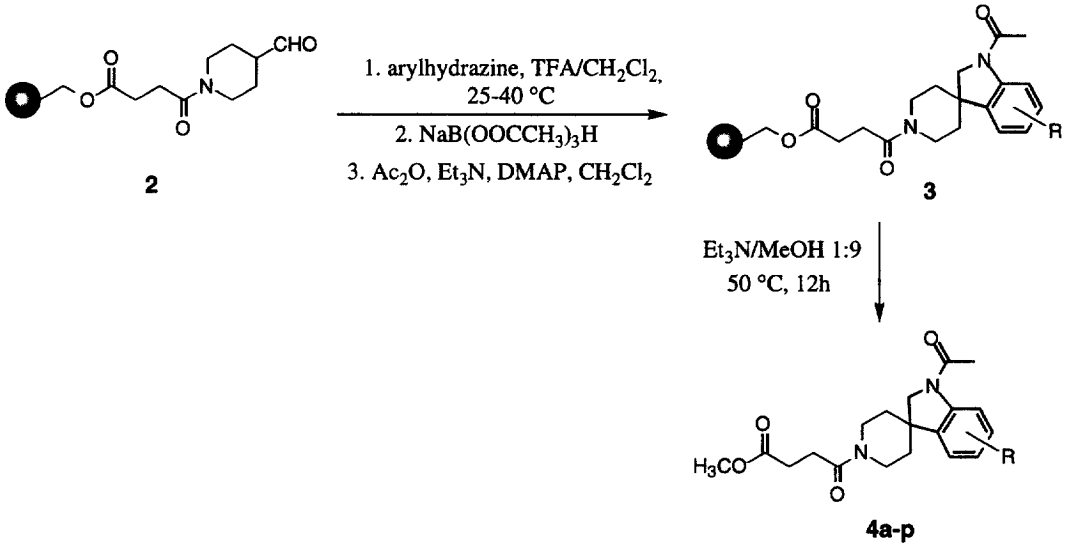
1

Rapp TentaGel resin with base-cleavable HMB (4-hydroxymethylbenzoic acid) handle was chosen as the solid support. The dimethyl acetal protected piperidine-4-carboxaldehyde was attached to the resin using standard coupling reactions *via* a succinic anhydride derived linker. The acetal group was removed under mild acidic conditions to afford the polymer bound aldehyde (**2**). The polymer bound aldehyde were then allowed to react with arylhydrazines in the presence of TFA in CH_2Cl_2 (Scheme 2).[5] Various arylhydrazines were studied in the Fischer indole reaction under the conditions described in the Table 1. After $NaB(OAc)_3H$ reduction of the indolenine intermediate and acylation with acetic anhydride, the spiroindoline products could then be cleaved

from the resin with (9:1) MeOH/Et_3N in good yields (83-95%). In most cases, the products were obtained in good to excellent chemical purity as determined by HPLC[6], ^1H NMR and MS analyses.

We investigated the effect of solvents and TFA concentrations on the Fischer indole reaction. Methylene chloride is the only solvent which gave desired products. In other solvents, such as 1,2-dichloroethane, tetrachloroethane, 1,1,1-trichloroethane or CH_2Cl_2/THF (1:1), no cyclization product was formed and only decomposition was observed. We also studied other conditions of indole synthesis on solid support[7], all of which gave complex mixtures and no desired product was obtained.

Scheme 2



2 **3** **4a-p**

A wide range of arylhydrazines react cleanly, demonstrating the flexibility of this procedure. With arylhydrazines having electron-withdrawing groups, a higher concentration of TFA (10-25%) was required for the reaction. Otherwise, no cyclization occurred and only hydrazones were observed. It was also important to exclude oxygen from the reaction when arylhydrazines with electron-donating groups were used since the hydrazones as well as indolenine intermediates were not stable.

In summary, a simple and direct method for solid phase synthesis of spiroindoline derivatives has been developed. The strategy is feasible for large variety of arylhydrazines, and is amenable for constructing combinatorial libraries with spiroindoline as a core structure.

Table 1. Synthesis of Spiroindolines with Arylhydrazines

Entry	Hydrazines	Reaction Conditions	Yield	HPLC Purity
4a	phenyl	2% TFA/CH_2Cl_2, 40 °C, 17h	95%	72%
4b	2-bromophenyl	10% TFA/CH_2Cl_2, 40 °C, 17h	93%	72%
4c	4-trifluoromethylphenyl	10% TFA/CH_2Cl_2, 40 °C, 17h	91%	83%
4d	3,5-dichlorophenyl	10% TFA/CH_2Cl_2, 40 °C, 17h	95%	79.4%
4e	3-nitrophenyl	10% TFA/CH_2Cl_2, 40 °C, 17h	87%	83%[a]
4f	4-nitrophenyl	25% TFA/CH_2Cl_2, 40 °C, 17h	94%	66%
4g	3,4-dichlorophenyl	10% TFA/CH_2Cl_2, 40 °C, 17h	94%	70%[a]
4h	2,4-dichlorophenyl	10% TFA/CH_2Cl_2, 40 °C, 17h	94%	70%[a]
4i	3,5-ditrifluoromethylphenyl	20% TFA/CH_2Cl_2, 40 °C, 17h	95%	66%
4j	4-*t*-butylphenyl	2% TFA/CH_2Cl_2, rt, 17h	95%	87%
4k	4-benzyloxylphenyl	2% TFA/CH_2Cl_2, rt, 17h	91%	87%
4l	2,5-dimethylphenyl	2% TFA/CH_2Cl_2, rt, 17h	89%	80%
4m	4-methoxyphenyl	2% TFA/CH_2Cl_2, rt, 17h	94%	67%
4n	4-trifluoromethoxyphenyl	4% TFA/CH_2Cl_2, 40 °C, 17h	87%	80%
4o	4-(2-oxazoly)phenyl	5% TFA/CH_2Cl_2, rt, 17h	83%	79%
4p	1-naphthyl	2% TFA/CH_2Cl_2, rt, 17h	95%	64%

[a] A combined purity of two isomers

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analysis.

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5. A typical procedure is as follows: 100 mg of Rapp TentaGel S HMB resin (0.25mmol/g) was added to a test tube capped with a rubber septum and suspended in 4 ml of 2-25% TFA/CH_2Cl_2. 200 µl Anisole was added to the suspension. The mixture was degassed with N_2 for 10 min, and arylhydrazine (10 equiv) was added. The mixture was degassed for another 10 min and then the reaction mixture was stirred under N_2 at 25-40 °C for 17h. A solution of 55 mg of $NaB(OAc)_3H$ in 1 mL of CH_2Cl_2 was added to the reaction *via* syringe. After the reaction mixture was stirred at room temperature for 0.5 h, the resin was transferred to a fritted vessel and washed with DMF (3×2mL), isopropanol (3×2mL) and CH_2Cl_2 (4×2mL). The cleavage is then performed with 3 mL of 9:1 MeOH/Et_3N at 50 °C overnight. The resin was removed by filtration and the sample was concentrated to dryness.

6. Analysis by HPLC using a 4 x 100 mm Zorbax SB-C8 column (5µ particle size) with a gradient of 10% acetonitrile/water containing 0.1 % TFA to 100% acetonitrile over 10 min. Peak areas were integrated at 220 nm.

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