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Optimization of spiroimidazolidinone derivatives synthesis on solid phase using SynPhase™ Lanterns

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Abstract—We report the synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives from *N*-benzyl-4-piperidone and *N*-protected amino acid amides on solid support. We have translated the chemistry from solution to solid phase using a backbone amide linker (BAL) mimic. Using a parallel combinatorial approach, we performed the optimization of the synthesis on SynPhase™ Lanterns.

Spiropiperidines belong to a relevant class of molecules for various G-protein coupled receptor targets and are often referred as 'privileged GPCR-structures'.[1] These derivatives which constitute high-functionalized templates could offer a useful structure for the discovery of new active compounds. We were particularly interested in 1,4,8-triazaspiro[4.5]decan-2-one derivatives (Fig. 1) which constitute conformationally restricted peptide surrogates but also novel scaffolds to design new drug-candidates.

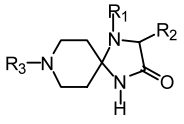
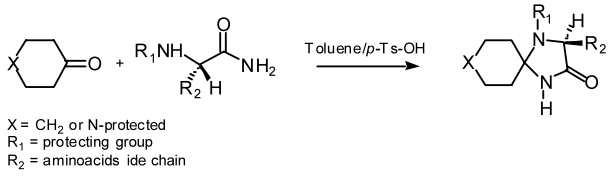


Figure 1. Structure of 1,4,8-triazaspiro[4.5]decan-2-one.



Scheme 1. Preparation of spiroimidazolidinone derivatives in solution.[2]

Until now, syntheses of spiroimidazolidinone analogues were exclusively performed in solution from a cyclic ketone and an *N*-protected amino acid amide[2] (Scheme 1). Due to the low yield obtained in solution syntheses and having as a main objective the preparation of a library of spiroimidazolidinone derivatives, we focused our efforts toward their synthesis on solid support. Consequently, combinatorial synthetic methods[3] for optimization of hits and rapid production of large sets of compounds appeared an effective approach.

For this purpose, we chose the Mimotope's Multipin[4] method which is currently used to rapidly explore a large range of reaction parameters in parallel experiments. The strategy consisted in the obtention of spiroimidazolidinones anchored to a BAL[5] linker mimic through the secondary amine as described in Scheme 2. Since purification of resin-anchored compounds is not possible, to achieve acceptable purity for a multistep library synthesis each reaction requires optimization. To quickly optimize the reaction conditions (solvent, temperature, reaction time,…) of each step, we used an internal probe[6] especially designed to evaluate the conversion percent by a single LC/MS analysis. In our case, this probe carried a carboxybenzaldehyde moiety which allowed reductive amination and, unlike BAL linker, is stable under acidic treatment. To perform our experiments, we used SynPhase™ Rink amide polystyrene L-series and polyamide D-series SynPhase™ Lanterns with a loading of 8 and 15 μmol, respectively. Fmoc-Ala-OH and Fmoc-Phe-OH (120 mM concentration) were successively coupled using HBTU (120 mM) in the presence of DIEA (240 mM) in DMF for 3 h. Subsequently, 4-carboxybenzaldehyde (200 mM con-

Keywords: spiroimidazolidinone; SynPhase™ Lanterns; backbone amide linker mimic; optimization.

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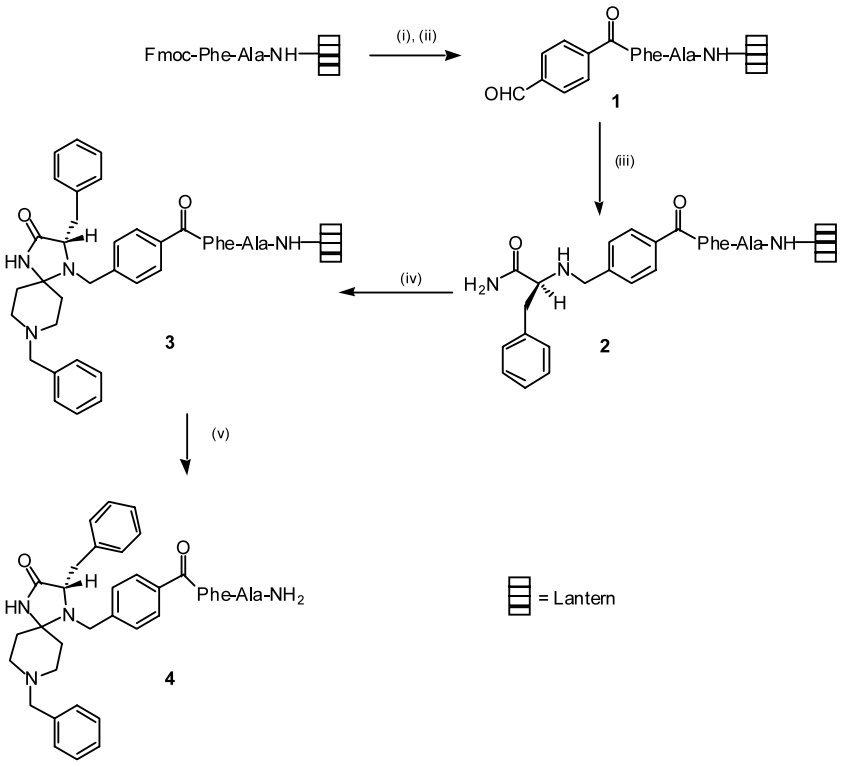

Scheme 2. *Reagents and conditions*: (i) 20% piperidine/DMF, 20 min for polyamide and 60 min for polystyrene Lanterns; (ii) HOOC-C_6H_5-CHO/HBTU/DIEA, 3 h; (iii) H-Phe-NH_2/$NaBH_3CN$/1% AcOH/DMF, 60°C, overnight; (iv) *N*-benzyl-4-piperidone, toluene/DMP (95/5), 1% *p*-TsOH, 80°C, 10 days; (v) TFA/H_2O/TIS (95:2.5:2.5).

centration) was allowed to react with HBTU (200 mM) and DIEA (200 mM) in DMF for 3 h to yield the probe linker OHC-C_6H_5-CO-Phe-Ala-Lantern (**1**). Deprotection steps were performed with a piperidine/DMF solution (20/80) in 60 min for polystyrene Lanterns and 20 min for polyamide Lanterns. The OHC-C_6H_5-CO-Phe-Ala-Lanterns **1** were then subjected to reductive amination by treatment with H-Phe-NH_2 (150 mM), used as a model amino acid amide in our experiment, in 1% AcOH/DMF in the presence of $NaBH_3CN$ (50 mM) to yield **2**.

We then optimized the key step of the synthesis which consisted in the condensation of the commercially available *N*-benzyl-4-piperidone onto the phenylalaninamide **2** anchored through its N^{α}-nitrogen to afford the cyclized compound **3**.

We examined eight parameters: solvent, *N*-benzyl-4-piperidone concentration, catalyst, reaction time, temperature, pressure, sonication and presence of a dehydrating agent (Table 1). In a first instance, we used toluene to explore all the parameters described in Table

Table 1. Cyclization step via various experimental conditions

Temperature	Solvent	[Ketone]	Catalyst	Others
40°C	DCM	0.1 M	No catalyst	P_2O_5
60°C	Acetone, CH_3CN, THF, MeOH,	1 M	AcOH 1%	$MgSO_4$
	EtOH	2 M	*p*-TsOH 1%	Molecular sieves
80°C	AcOEt, DMP, NMP, DME,	5 M	*p*-TsOH 10%	Sonication
	$(CH_3)_2CHOH$, ethyleneglycol,	10 M		10 kbar
	cyclohexane, toluene, DMF,			
	dioxane, xylene, pyridine,			
	butanol			
80°C	Toluene/DMP 99/1			
	Toluene/DMP 95/5			
	Toluene/DMP 90/10			
	Toluene/DMP 85/15			
	Toluene/DMP 70/30			
	Toluene/DMP 50/50			

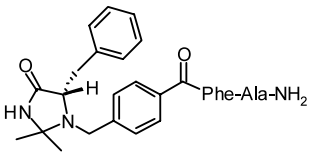

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Figure 2. By-product **5**.

1 and performed a kinetic study (1 to 10 days). A total of 100 different conditions were examined. The stacked disks that constitute the Lanterns were cut with a scalpel for kinetic monitoring. TFA cleavages were performed and relative percentage conversion[7] to spiroimidazolidinone **4** was determined. The best conditions for this primary optimization were 1 M *N*-benzyl-4-piperidone in the presence of 1% *p*-TsOH for 10 days at 80°C. However, only 30% conversion was obtained. We then analyzed a large set of solvents (18) in these optimal conditions. 2,2 Dimethoxypropane (DMP) gave the higher percentage conversion (75%) and no initial compound was detected by HPLC. However, a by-product, the 4-imidazolidinone **5** (Fig. 2) was obtained after the final TFA cleavage. This compound was produced by the condensation of DMP onto **2**. To increase the percentage conversion and to decrease the secondary reaction observed with DMP, we carried out the reaction in various mixtures of toluene/DMP associated with a kinetic study (1 to 10 days). The best result was obtained by treatment of **2** with 1 M *N*-benzyl-4-piperidone in toluene/DMP (95/5), in the presence of 1% *p*-TsOH for 10 days at 80°C providing after TFA cleavage compound **4** with a 95% purity established by HPLC. The yield calculated from the initial Lantern loading was of 90%.

In conclusion, we have developed a strategy on solid support to obtain 1,4,8-triazaspiro[4.5]decan-2-one derivatives in high yield and purity. The spiroimidazolidinone formation was optimized by systematically varying reaction parameters such as solvent, concentration reagents, catalyst, and reaction time. Results concerning the solvent pointed out the significance of using DMP that could play the role of dehydrating reagent. On the other hand, no significant difference in purity and yield was observed between polystyrene and polyamide support. Application of this strategy on BAL linker and generation of spiroimidazolidinone compound libraries is under investigation.

Acknowledgements

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7. Based on HPLC peak areas at 214 and 254 nm of compound obtained after TFA cleavage of **2** and **3**.