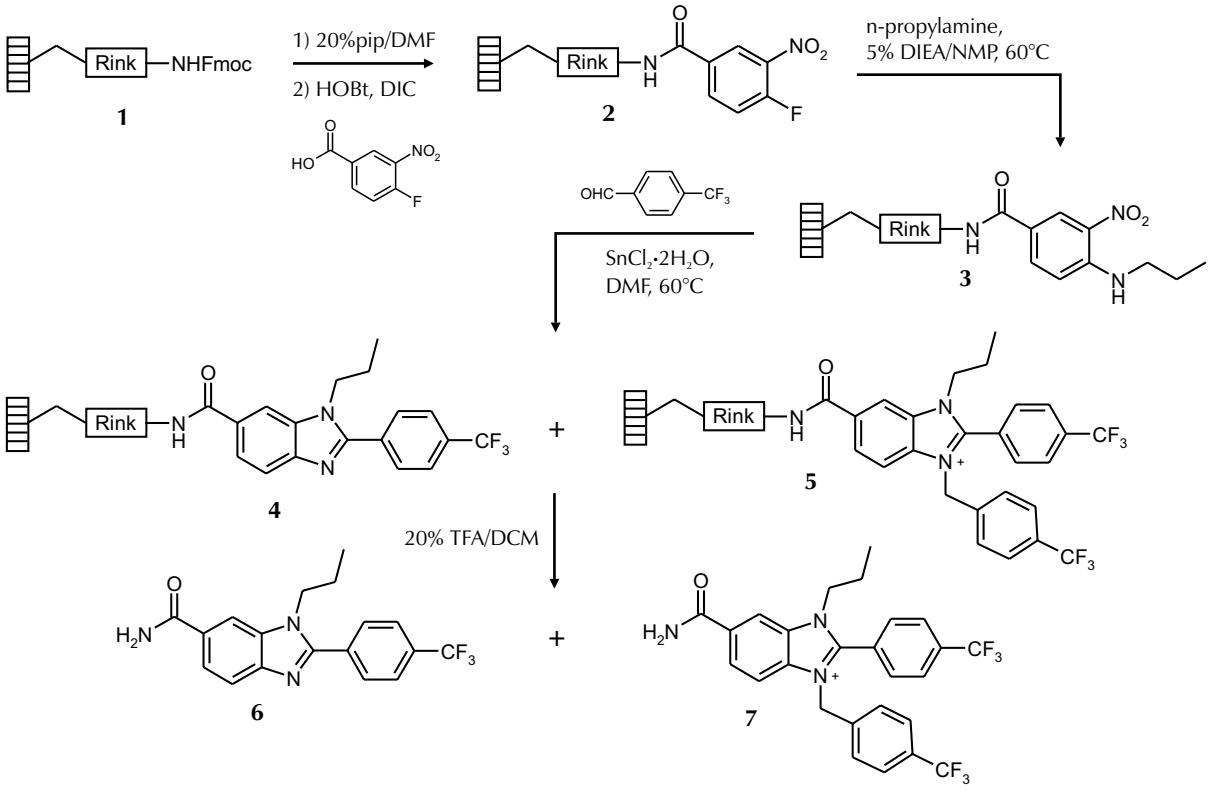
Solid Phase Synthesis of Benzimidazoles: A Comparative Study on SynPhase™ A-, D- and L-series Lanterns

SynPhase A-series Lanterns are the latest addition to the SynPhase product range and offer a higher loading than L- and D-series Lanterns. All three series offer the same performance in terms of kinetics, yield and purity, and chemistry transfers between the different Lantern types without the need for re-optimization.

This technical note demonstrates the ease of chemistry transfer using a one-pot reduction-cylization synthesis of benzimidazoles, previously developed by Mimotopes on SynPhase PS D-series Lanterns[1].

Materials and Methods



DCM:	dichloromethane	pip:	piperidine
DIC:	*N,N'*-diisopropylcarbodiimide	DIEA:	diisopropylethylamine
DMF:	dimethylformamide	TFA:	trifluoroacetic acid
Fmoc:	9-fluorenylmethoxycarbonyl	NMP:	1-methyl-2-pyrrolidinone
HOBt:	*N*-hydroxybenzotriazole (monohydrate)		

Reagent Preparation

SynPhase PS Fmoc Rink amide L-, D- and A-series Lanterns (15 each, loading 15, 35, 75μmol respectively) in a reaction flask were treated with 20% piperidine (30mL) at room temperature for 45min. The reagent solution was decanted and Lanterns washed with DMF (3×3min), DCM (3×3min) and air dried.

The Fmoc deprotected Lanterns were treated with 30mL of a solution of 4-fluoro-3-nitrobenzoic acid (0.15M), DIC (0.15M) and HOBt (0.075M) in 20% DMF/DCM at room temperature for 16h. The reagent solution was decanted and Lanterns washed with DMF (3×3min), DCM (3×3min) and air dried to give the Lantern-bound **2**.

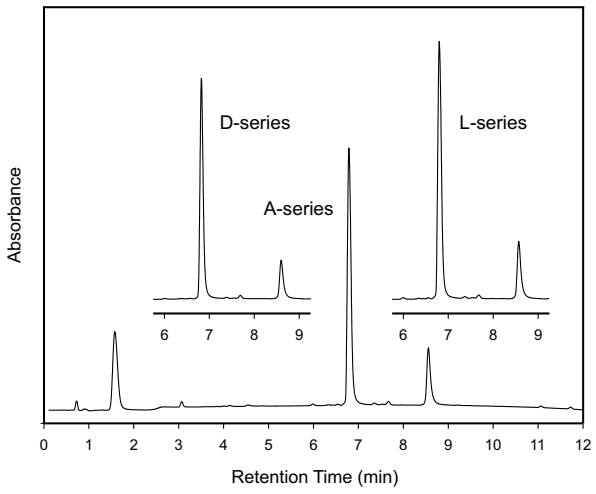
Lanterns **2** were treated with 30mL of a solution of n-propylamine (0.5M) in 5% DIEA/NMP at 60°C for 16h. The solution was decanted and Lanterns washed with DMF (3×3min), DCM (3×3min) and air dried to give the Lantern-bound **3**.

Four Lanterns each of L-, D- and A-series **3** were treated with (1.0, 2.0 & 4.0mL respectively) of a solution of tin(II) chloride dihydrate (0.75M) and 4-(trifluoromethyl)benzaldehyde (0.14M, 2 eq) in DMF at 60°C for 16h. The reagent solution was decanted and Lanterns washed with DMF (3×3min), DCM (3×3min) and air dried to give the Lantern-bound **4** and **5**. Each group of 4 L-, D- and A-series Lanterns was cleaved with 20% TFA/DCM (2.0, 3.0 & 4.0 mL respectively) at room temperature for 1h. The cleavage solution was evaporated to dryness . The residue was dissolved in 10% H_2O/CH_3CN for HPLC and LC-MS analysis.

Results and Conclusion

All benzimidazole products **6** obtained from three different types of Lanterns gave nearly identical HPLC chromatograms and purities. The purity of the products were 76 (19)%, 78 (17)% and 74 (19)% corresponding to L-, D- and A-series Lanterns respectively. The figures in parentheses indicate the percentage of the by-product benzimidazolium **7**. Both the benzimidazole **6** and benzimidazolium **7** are confirmed by LC-MS. The yield was >95% in all cases.

The one-pot benzimidazole synthesis on SynPhase Lanterns has demonstrated that the chemistry developed on a particular series of Lanterns (D-series in this case) can be freely transferred between L-, D- and A-series Lanterns without comprise of results.



Reverse phase HPLC trace of a crude benzimidazole product synthesized on A-, D- and L-series Lanterns under identical conditions.

Detection at 214nm

References

1 Wu, Z., Rea, P., Wickham, G., Tetrahedron Letters, 2000, **41**, 9871-9874.

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