Solid Phase Sonogashira Reactions on Mimotopes' SynPhase™ Grafted Supports using the Argonaut Quest™ 210 Synthesizer

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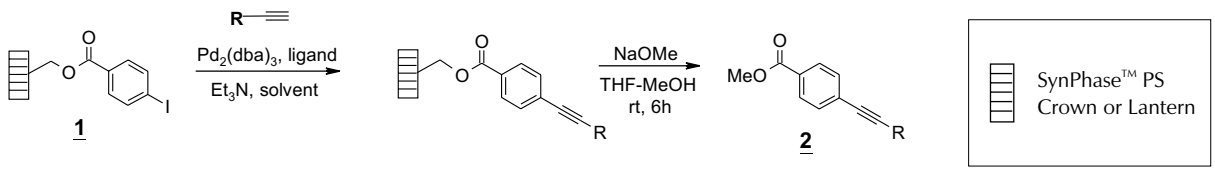
The Sonogashira reaction, a palladium catalyzed cross-coupling reaction, was performed on Mimotopes' SynPhase™ I-Series polystyrene-grafted Crowns using an Argonaut Quest 210 synthesizer. The aryl halide component was immobilized on the solid phase and subsequently reacted with acetylenes and catalyst. The SynPhase crowns were easily handled and washed in the Quest 210 as filtration steps were eliminated.



Introduction

SynPhase functionalized surface grafted shaped supports (I-Series Crowns and new D- and L-Series Lanterns) are an attractive alternative to using resin in solid phase combinatorial chemistry[1] and in particular in automated synthesizers such as the Argonaut Quest 210.[2] Substitution of Crowns or Lanterns for resin eliminates tedious weighing and filtration steps. The Sonogashira reaction is an important solution phase Pd catalyzed C-C bond-forming reaction.[3,4] In this solid phase application, the reaction between selected acetylenes and 4-halobenzoic acid immobilized as the ester on chloromethyl functionalized polystyrene SynPhase I-Series Crowns was explored. The products were released from the solid phase by transesterification in good to excellent yields (**Table**).

Table | Optimization of Sonogashira Reaction on SynPhase Crowns

Entry	Halide	R group	Solvent	Ligand	Pd(mol%)	Temp(^{0}C)	Time(h)	Yield(%)
1[a]	**I**	**Ph**	**THF-Et_3N(1:1)**[5]	**Ph_4PCl**	**30**	**60**	**17**	**96**
2[a]	**I**	**CH_2CH_2OH**	**THF-Et_3N(1:1)**[5]	**Ph_4PCl**	**30**	**60**	**17**	**88**
3	Br	Ph	THF-Et_3N(1:1)[5]	$P(2\text{-Tol})_3$	30	100	12	86
4	I	Ph	THF-Et_3N(1:1)[5]	$P(2\text{-Tol})_3$	30	60	21	76
5	I	Ph	THF-Et_3N(1:1)[5]	Ph_4PCl	30	60	21	75
6	Br	Ph	THF-Et_3N(1:1)[5]	Ph_4PCl	30	100	12	69
7[a]	I	^{n}Bu	THF-Et_3N(1:1)[5]	Ph_4PCl	30	60	17	39
8	Br	Ph	THF-Et_3N(1:1)[5]	$P(2\text{-Tol})_3$	30	60	20	31
9	Br	Ph	1,4-Dioxane	$P(2\text{-Tol})_3$	30	100	26	Nil[b]
10	I	Ph	DMF	Ph_4PCl	50	100	48	Nil[c]

a: Reaction performed in Quest 210; b: mixed product; c: Methyl 4-iodobenzoate was isolated

Experimental Section

SynPhase PS I-Series chloromethyl Crowns (50 pieces, 20.4μmol each) were reacted with Cs_2CO_3 (2.00g, 6.12mmol, 5eq), KI (170mg, 1.02mmol, 1eq) and 4-halobenzoic acid (3.06mmol, 3eq) in DMF (100mL) with gentle stirring at 80°C for 24h to give **1**. The Crowns were washed with DMF, water then THF followed by drying under reduced pressure.

Loading determination. The halobenzoate SynPhase Crowns **1** (two pieces) and 28% NaOMe in MeOH, (0.305mmol, 0.061mL) in THF-MeOH (2:1) (5.7mL) were stirred at room temperature for 6h. The Crowns were removed from the mixture and the solution was diluted with water (20mL) then extracted with ether aliquots (3×30mL). The ethereal phase was dried with $MgSO_4$ and evaporated under reduced pressure. The crude material in each case was purified by silica gel column chromatography using hexane-ethyl acetate (30:1) to give pure methyl 4-halobenzoate (for halo: 20.0-20.4 μmol/piece; Bromo: 20.4 μmol/piece).

Sonogashira reaction. In a typical experiment, **1** (2 pieces, 40.8μmol) were placed into a 5mL Teflon™ reaction vessel on the Quest 210. Catalyst ($Pd_2(dba)_3$, 5.61mg, 6.1μmol), Ph_4PCl (27.53 mg, 73μmol) and an acetylene (0.410mmol) were manually added followed by THF-Et_3N (1:1, 3.5mL). The reaction tube was agitated on the Quest 210 for 17h at 60°C. The tube was then cooled to room temperature and the Crowns isolated from the reaction mixture. The SynPhase Crown was washed with DMF, water, and THF on the Quest. The product **2** was cleaved from the support by treatment of the crown with 28% NaOMe in MeOH and THF-MeOH (2:1) as described above. After dilution with water, the mixture was extracted with ether aliquots to give crude material which was further purified by silica gel column chromatography (hexane: ethyl acetate 30:1) to give pure acetylene products **2** (**Table**).

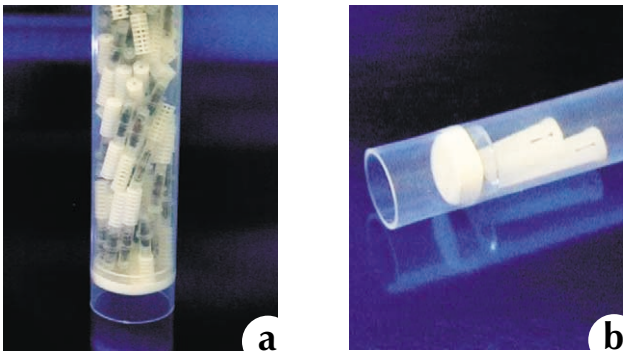


Fig 1 Quest reaction vessels with:
a) SynPhase Lanterns tagged with TranStems
b) SynPhase Crowns

Results and Summary

The Table shows that optimized Sonogashira reactions on the SynPhase PS Crown surface deliver good to excellent yields of acetylene products after cleavage from the solid phase. Reactions in the Quest 210 are particularly easy to conduct as washing of the Crowns involves no filtration steps and this process can be automated. Library synthesis can be accommodated on the Quest by utilizing directed sorting strategies with TranSort™ transponder tagging in tandem with SynPhase Crowns[2] and the more recently commercially released SynPhase Lanterns.

The work in this study was performed on SynPhase I-series Crowns. This product has been replaced by SynPhase L- and D-Series Lanterns, which provide greatly improved reaction kinetics and higher loadings. The chemistry described here using the SynPhase I-Series Crowns is easily adaptable to the SynPhase L- or D-Series Lanterns.

References

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