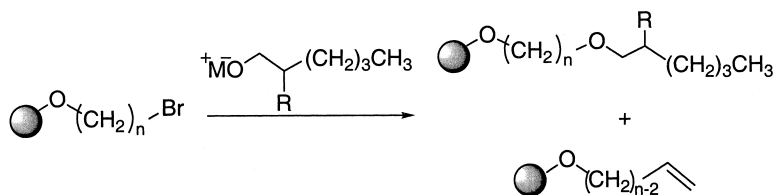Report

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Williamson Ether Synthesis on Solid Support: Substitution versus Elimination

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The revival of solid-phase organic synthesis (SPOS) observed in the past decade was inspired by the emergence and enhanced development of combinatorial techniques for drug discovery.[1] While most reports involving SPOS are sharply target-oriented and narrowly focused, fewer works could be seen as basic studies on SPOS methods. Some organic reactions underwent excellent adaption to solid support and are regularly used in SPOS.[2] However, the majority of the reactions known in solution are only occasionally utilized (if at all), and their generality and applicability to synthesis on solid support remains questionable.

The Williamson reaction in solution has been known for almost 150 years and represents one of the main methods of ether linker construction.[3] Being a typical aliphatic nucleophilic substitution, the reaction is sensitive to a variety of parameters, such as solvent, temperature, the nature of the leaving group, the nucleophile, and the counter cation.[4] Additives (e.g., crown ethers and iodide salts) were used for the reaction promotion.[5] The applications of Williamson ether synthesis on solid support are mostly limited to the simplest case of benzyl halide substitution.[6] However, the more problematic substitutions of aliphatic halides are hardly found.[7] No true estimation of the reaction outcome as a function of condition parameters was ever reported.

Since one of our projects requires an efficient bis-aliphatic ether synthesis step, we decided to take a closer look at the Williamson reaction on solid support.

In a series of experiments, a substitution of a resin-bound ω-bromo alcohol with two primary alkoxides (derived from 1-hexanol and 2-ethyl-1-hexanol) was examined (Scheme 1).

Compounds **1** were prepared by immobilizing the appropriate bromo alcohol on the Wang trichloroacetimidate resin (**1a**, **1b**, **1d**−**1f**)[8] or by reacting the deprotonated Wang resin with the appropriate dibromide (**1c**).[7] Following the Williamson reaction, the resins were subjected to acidic cleavage (TFA/CDCl$_3$ 1:1 v/v mixture), and the filtrates were analyzed by ^{1}H NMR.[9] The S$_N$/E ratio was derived from the integration ratio of the clear signals of -CH$_2$-O-CH$_2$- moiety belonging to the cleaved substitution product **5** (d + t or t + t at 3.6−4.0 ppm) vs the clear signals of the -CH=CH$_2$ moiety of the cleaved elimination product **6** (two multiplets at 5.0−5.9 ppm).

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The initial experiments were performed on Wang resin-immobilized 3-bromopropananol (**1b**) and 6-bromohexanol (**1d**). All experiments with **1b** and, to a lesser extent, **1d** exhibited a severe elimination of HBr accompanying the substitution. This observation markedly demonstrates the difference between the reaction in solution and on solid support. In solution chemistry, the elimination mostly accompanies the Williamson substitution of secondary and tertiary, but not primary, alkyl halides.[3,4] NMR estimations of the reaction outcome demonstrated that while the consumption of the bromo alcohol is almost always quantitative, the substitution/elimination ratio is strongly dependent on the reaction conditions.
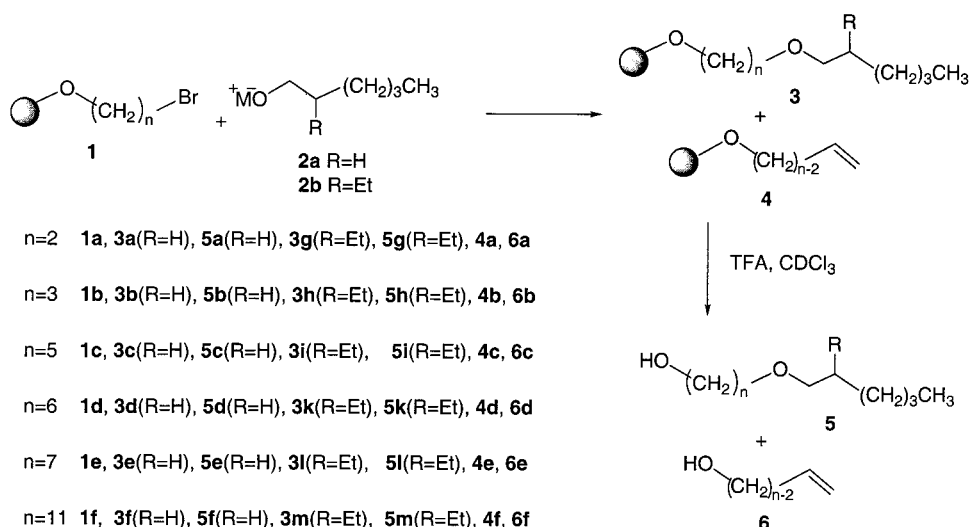
Thus, a parallel reaction condition screening experiment utilizing a 40-well robotic synthesizer was executed on resins **1b** and **1d**[10] (Table 1). Two primary alkoxides served as nucleophiles in the experiment: a linear one (**2a**) and a β-branched alkoxide (**2b**). The variable parameters in the experiment were the solvent, the base, and the additives. Since the initial experiments indicated that the presence of iodide salts and crown ethers improves the outcomes, the screening was performed mostly with iodide and crown ether additives. In parallel, or following the automated screening, a series of control manual experiments was performed (Table 2). While all the manually performed experiments confirm the tendencies observed using robotic screening, there is always a difference between the otherwise identical (or very similar) experiments. The substitution/elimination ratio is always substantially higher for the manual setup. (See, for example, entry 11 in Table 1 vs entry 6 in Table 2). The difference is attributed mostly to the different mixing techniques: while, in manual experiments, gentle magnetic stirring was employed, in robotic screening, shaking at 500 rpm was applied.

Still, since all the tendencies observed with the parallel screening were preserved in a series of selected, manually set-up experiments, the significance of the parallel screening data remains uncompromised.

The results of the screening demonstrated, not suprisingly, that the S$_N$/E ratio is sensitive to the steric size of the nucleophile, i.e., even the β-branching of **2b** reduces the ratio substantially (Table 1: entry 1 vs entry 2; Table 2: entries 2 vs 1 and 4 vs 3). The solvents of choice are DMA and NMP, while DMF is slightly inferior to them (Table 1: entries 7, 10, 11). Severe solubility problems were observed when attempts were made to perform the reaction in less polar solvents. The influence of additives is complicated and not entirely consistent. While the difference between a number of crown ethers is not significant, 15-crown-5 seems to be the best choice for most of the applied conditions (Table 1: entries 4−9; Table 2: entries 5, 6). Absence of crown ether, however, results in a significant drop in selectivity (Table 2: entry 8). Interestingly, when both the crown and the iodide salt are omitted from the reaction mixture, the selectivity increases (although the bromide conversion is

Scheme 1

n=2   **1a**, **3a**(R=H), **5a**(R=H), **3g**(R=Et), **5g**(R=Et), **4a**, **6a**

n=3   **1b**, **3b**(R=H), **5b**(R=H), **3h**(R=Et), **5h**(R=Et), **4b**, **6b**

n=5   **1c**, **3c**(R=H), **5c**(R=H), **3i**(R=Et),   **5i**(R=Et), **4c**, **6c**

n=6   **1d**, **3d**(R=H), **5d**(R=H), **3k**(R=Et), **5k**(R=Et), **4d**, **6d**

n=7   **1e**, **3e**(R=H), **5e**(R=H), **3l**(R=Et),   **5l**(R=Et), **4e**, **6e**

n=11   **1f**,   **3f**(R=H), **5f**(R=H), **3m**(R=Et),   **5m**(R=Et), **4f**, **6f**

Table 1. Automated Optimization Experiments[a]

entry	Nu	bromide	base	solvent	additive 1	additive 2[b]	selectivity[c]
1	**2b**	**1b**	NaH	NMP	TBAI	18c6	0.50
2	**2a**	**1b**	NaH	NMP	TBAI	18c6	0.79
3	**2a**	**1b**	^{t}BuLi	NMP	TBAI	15c5	1.08
4	**2b**	**1d**	NaH	DMA	KI	18c6	1.31
5	**2b**	**1d**	NaH	DMA	KI	18dbc6	1.22
6	**2b**	**1d**	NaH	DMA	TBAI	18dbc6	1.28
7	**2b**	**1d**	NaH	DMA	TBAI	15c5	1.47
8	**2b**	**1d**	NaH	DMA	TBAI	15c5[d]	1.20
9	**2b**	**1d**	NaH	DMA	KI	15c5[d]	1.25
10	**2b**	**1d**	NaH	DMF	TBAI	15c5[d]	1.12
11	**2b**	**1d**	NaH	NMP	TBAI	15c5	1.44
12	**2b**	**1d**	KH	DMA	TBAI	18c6	0.55
13	**2b**	**1d**	KH	DMA	KI	18dbc6	0.52
14	**2b**	**1d**	KH	DMA	KI	15c5	0.56
15	**2b**	**1d**	^{t}BuLi	NMP	TBAI	15c5	1.66

[a] Reaction conditions: **2** (6 equiv), base (6 equiv), additives (1 equiv), room temperature, 6 h. [b] 18c6 = 18-crown-6; 15c5 = 15-crown-5; 18dbc6 = dibenzo-18-crown-6. [c] Substitution/elimination products ratio. [d] Catalytic amount (0.1 equiv).

Table 2. Manual Optimization Experiments[a]

entry	Nu	bromide	base	solvent	additive 1	additive 2[b]	selectivity[c]
1	**2a**	**1b**	NaH	DMA	TBAI	18c6	1.08
2	**2b**	**1b**	NaH	DMA	TBAI	18c6	0.65
3	**2a**	**1d**	NaH	DMA	TBAI	18c6	2.80
4	**2b**	**1d**	NaH	DMA	TBAI	18c6	2.02
5	**2b**	**1d**	NaH	NMP	TBAI	18c6	2.04
6	**2b**	**1d**	NaH	NMP	TBAI	15c5	2.11
7	**2b**	**1d**	NaH	NMP			1.97
8	**2b**	**1d**	NaH	NMP	TBAI		1.69
9	**2b**	**1d**	NaH	NMP	CsI		1.40
10	**2b**	**1d**	^{t}BuLi	DMA	TBAI	15c5	2.35
11	**2b**	**1d**	NaH	NMP	LiI	15c5	2.50

[a] Reaction conditions: **2** (6 equiv), base (6 equiv), additives (1 equiv), room temperature, 6 h. [b] 18c6 = 18-crown-6; 15c5 = 15-crown-5; 18dbc6 = dibenzo-18-crown-6. [c] Substitution/elimination products ratio.

slowed in this case) (Table 2: entry 7). Regarding the iodide salts, no substantial difference was observed between TBAI and KI (Table 1: entries 5 vs 6, 8 vs 9), while CsI has a detrimental effect on the selectivity (Table 2: entry 9 vs 8).

The negative effect of cesium is closely related to other important observations examining the influence of the cation on the substitution selectivity. Here again, a striking difference from the solution chemistry is observed. In solution, absence of small cations in the reaction mixture, in polar aprotic solvents, usually results in enhancement of the substitution, attributed to the generation of "naked" nucleophiles.[5b,11] The results of the screening experiment demonstrate that, although the reaction is performed in polar aprotic solvents, the presence of Na$^+$ dramatically increases the substitution/elimination ratio compared to the reactions where solely bigger K$^+$ and Bu$_4$N$^+$ cations are present (Table 1: entries 4 vs 12, 7 vs 14, 5 vs 13). This is an unprecedented observation in regard to a nucleophilic substitution reaction. To further pursue the exploration of this interesting phenomenon, we separately performed a number of experiments with Li$^+$ ions present in the reaction mixture (Table 1: entries 3, 15 and Table 2: entries 10, 11). The results of these experiments follow the aforementioned trends. Thus, using ^{t}BuLi as a base, under otherwise similar conditions, the substitution/elimination ratio reached 1.08 for the **1b** resin and 1.66 (automated) or 2.35 (manual) for the **1d** resin, while with Na$^+$ as the smallest cation in the mixture the corresponding values are 0.79, 1.44, and 2.11, respectively. With K$^+$/NBu$_4^+$ only, the observed ratios for the resin **1d** are 0.5– 0.6. Moreover, it seems that Li$^+$, added as iodide salt and not as the base counter cation, improves the selectivity even more (Table 2: entry 11 vs 10).

The most striking effect, already observed at the initial stage of our study, is the strong dependence of the substitution/elimination ratio on the length of the immobilized bromo alcohol. The dramatic difference observed for the bromohexanol vs bromopropanol (Table 1: 1.31 vs 1.08; Table 2: 2.80 vs 1.08, 2.02 vs 0.65) inspired us to test this dependence for some additional bromo alcohols. This series of experiments clearly demonstrates that the longer the bromo alcohol, the more favorable the substitution/elimination ratio becomes (Table 3).[12] Since no electronic or steric effect, connected to the bromo alcohol structure, could be held responsible for this effect, it must be the polymer-matrix "proximity" effect. A reasonable explanation of the effect is that most of the support reactive sites are not fully solvated but, rather, placed in the apolar environment of the polystyrene. Indeed,

Table 3. Influence of the Alkyl Spacer Chain Length on Selectivity[a]

entry	Nu	bromide	selectivity[b]
1	**2b**	**1a**	0.33
2	**2b**	**1b**	0.50
3	**2b**	**1c**	0.85
4	**2b**	**1d**	1.31
5	**2b**	**1e**	1.73
6	**2b**	**1f**	3.00
7	**2a**	**1a**	0.42
8	**2a**	**1b**	0.79
9	**2a**	**1c**	1.13
10	**2a**	**1e**	2.10
11	**2a**	**1f**	>20[c]

[a] Reaction conditions: NMP, **2** (6 equiv), NaH (6 equiv), TBAI (1 equiv), 18-crown-6 (1 equiv), room temperature, 6 h. [b] Substitution/elimination products ratio. [c] Insignificant traces of elimination product.

it is known that an apolar environment favors elimination rather than substitution.[13] The more extended the bromoalkyl chain, the more solvated the reaction site and the less the influence of the apolar polymer on the reaction's course.

The conclusions from the data gathered on the solid-phase Williamson reaction are both practical and conceptual.

From a practical point of view, it is clear that, for successful Williamson ether synthesis, a long spacer/linker is required (more than 10 atoms). In addition, utilization of NMP or DMA as a solvent, Li$^+$ cation presence, and 15-crown-5 and iodide salt addition are recommended for high-yielding substitution. Stirring must be preferred over shaking. The efficiency of substitution can be substantially improved even for relatively short spacers/linkers (6–10 atoms) if the combination of these optimal conditions is applied.

In light of the significant elimination observed for short spacers, it is possible that the same products can be obtained more efficiently by reacting supported alkoxides with an excess of soluble alkyl halides.[7] Unfortunately, this strategy has not yet been optimized and, according to our experience, produces only moderate yields.

The more general conclusions are that, in addition to the obvious change of reaction conditions from homogeneous to heterogeneous, imposed by the transition from solution to solid phase synthesis, the reaction outcomes can be strongly influenced by unexpected effects, presumably imposed by the polymer matrix. Thus, optimization basic studies of the reactions on solid support can be both essential and highly rewarding.

Supporting Information Available. Representative NMR spectra, general experimental procedures for immobilization and cleavage, as well as the optimized etherification procedure are available free of charge via the Internet at http://pubs.acs.org.

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