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Reactions of aldehydes with polymer-supported selenoalkylidenetriphenylphosphoranes. A facile method for the synthesis of carbonyl compounds†

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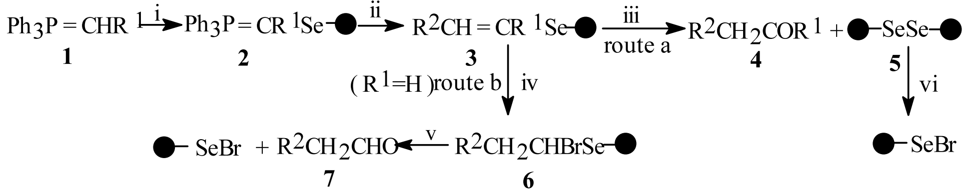
Abstract—The transylidation reactions of polymer-bound selenium bromide with alkylidenetriphenylphosphoranes **1** gave resin **2**, which is sufficiently reactive to undergo Wittig-type reactions to afford the vinylic selenide resins **3**. Cleavage gave ketones and aldehydes under different conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Solid-phase organic synthesis has been widely used in the preparation of a large number of structurally diverse compounds for combinatorial libraries.[1] By using this technique, the purification of the organic products has been greatly simplified through the use of polymeric resins. The use of organoselenium reagents in organic synthesis is now commonly accepted as a useful tool for introducing new functional groups into organic substrates under extremely mild reaction conditions.[2] Vinylic selenides, in particular, are intermediates with great synthetic potential. The first systematic approach to the synthesis of vinylic selenides was the Wittig reaction between phenylselenoalkylidenetriphenylphosphoranes and aldehydes,[3] and their first synthetic utility was provided by their hydrolysis to ketones in the presence of $HgCl_2/CH_3CN/H_2O$[3] or TFA[4] in high yield. Aldehydes can also be obtained by reaction of 1-phenylseleno-2-alkenynes with hydrogen bromide followed by solvolysis in anhydrous DMSO.[5] However, these strategies for the synthesis of the carbonyl compounds are time-consuming and can not be automated. Recently, Nicolaou et al. reported the preparation of a polymer-bound selenium bromide[6a] and its application in organic synthesis.[7] Stimulated by these results, we attempted to use polymer-bound selenium bromide to carry out these reactions (Scheme 1) to find a facile way for the synthesis of ketones and aldehydes on solid phase.

Stirring a suspension of the selenenyl bromide resin with an alkylidenetriphenylphosphorane **1** in THF at room temperature resulted in rapid decolorization of the resin. The corresponding phosphonium salt formed via the transylidation reaction was not isolated before the Wittig step, which did not affect the final yields



Scheme 1. Solid-phase synthesis of ketones and aldehydes. *Reagents and conditions*: (i) ●–SeBr, THF, rt, 30 min; (ii) R^{2}CHO, THF, reflux, 2 h; (iii) 25% TFA/DCM, rt, 4 h; (iv) HBr, DCM, rt, 4 h; (v) DMSO, THF, rt, 1 h; (vi) Br_2, $CHCl_3$, rt, 30 min.

Keywords: solid-phase organic synthesis; Wittig reaction; ketone; aldehyde.

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(Table 1). The polymer-supported selenophosphorane **2** containing 0.96–0.97 mmol P/g was treated with an aldehyde to form a yellow vinylic selenide resin **3** containing 1.15–1.16 mmol Se per gram (9.1–9.2% Se) and no phosphorus by microanalysis. The infrared spectrum of the resin **3** showed strong C=C absorptions at 1600 and 1584 cm^{-1}. In the IR spectrum of the resin containing the nitro-group, there were two strong peaks, for NO_2, at 1521 and 1452 cm^{-1}. On treatment of the resin **3** with $HgCl_2/CH_3CN/H_2O$, no cleavage took place. Cleavage with TFA gave low yields and purities of the final products. After some screening, we found that when TFA/CH_2Cl_2 (1/10) was used, the expected ketones were obtained in good yields and high purities.[8] When R^1 was larger than CH_3, the yields of ketones (**4f** and **4g**) were poor.

The vinylic selenide resin **3**, where R^1 was hydrogen, did not hydrolyze to an aldehyde under the above transformation conditions. However, hydrolysis could be easily achieved by reacting the vinlyic selenide resin **3** with dry hydrogen bromide in DCM, followed by solvolysis to the corresponding aldehyde in the presence of anhydrous DMSO.[9] At the same time, the polymer-supported selenium bromide could be regenerated.

When the hydrolysis cleavage of resins **3** was used (**route a**), a deep yellow diphenyl diselenide resin **5** was obtained after washing and drying and its infrared spectrum included an Se–Se absorption at 1260 cm^{-1}. Treatment of the resin **5** with Br_2 in $CHCl_3$ for 30 min at room temperature afforded the polymer-bound selenium bromide as red beads, which possessed infrared spectroscopic data identical to those of the initial selenenyl bromide resin. The loading of the resin **5** was 1.12–1.15 mmol Se/g, which was confirmed by the analysis of the recovered selenenyl bromide resin containing 1.10–1.15 mmol Br/g. These results indicated that the Se–Se bonds must be present in the resin **5**. The recovered selenenyl bromide resin was then reused in the preparation of carbonyl compounds. For example, ketone **4a** was obtained in 74% yield under the same reaction conditions (second run), and in 70% yield after the second recycle (i.e. third run). During the course of these successive runs, the color of the selenenyl bromide resin gradually changed from deep red to red. It was shown that recycling 2–3 times led to a gradual deterioration of the resin.

Table 1. The yield and purity of ketones and aldehydes[a]

Entry	R^1	R^2	Yield (%)[b]	Purity (%)[c]
4a	CH_3	C_6H_5	80	90
4b	CH_3	p-$CH_3C_6H_4$	77	92
4c	CH_3	p-$NO_2C_6H_4$	82	93
4d	CH_3	p-Cl C_6H_4	78	91
4e	CH_3	$CH_3(CH_2)_2$	70	88
4f	C_2H_5	C_6H_5	45	—
4g	C_6H_5	C_6H_5	40	—
7a	H	C_6H_5	76	90
7b	H	p-$CH_3C_6H_4$	78	91
7c	H	p-$NO_2C_6H_4$	75	93
7d	H	p-ClC_6H_4	72	90
7e	H	p-$CH_3OC_6H_4$	72	91
7f	H	$CH_3(CH_2)_2$	73	90

[a] All compounds are known and their structures were determined by ^1H NMR and IR.

[b] Overall yields based on selenenyl bromide resin (1.18 mmol/g).

[c] Determined by ^1H NMR of the crude cleavage product.

In conclusion, we have developed a SPOS route to ketones and aldehydes in good yields and purities. Although an excess of the reagents is required, simple work-up procedures take the place of the time-consuming isolation and purification steps in the solution-phase synthesis.

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8. General procedure for the solid-phase synthesis of ketones: The polystyrene-bound selenenyl bromide (1.0 g) prepared from polystyrene (cross-linked with 1% divinyl benzene) as described in the literature,[6a] was swelled in THF for 30 min at room temperature. A solution of the alkylidenetriphenylphosphorane prepared from alkyltriphenylphosphonium bromide (1.2 mmol) and *n*-BuLi (in hexane 1.2 mmol) in 10 ml of THF under a nitrogen atmosphere, was added and the mixture was stirred for an additional 30 min at room temperature. The aldehyde (1.5 mmol) was added and the mixture was refluxed for 2 h. Then it was cooled to room temperature and filtered, the resin was washed successively with C_6H_6, H_2O, THF, CH_3OH, DCM, Et_2O (2×5 ml of each) and then dried under vacuum to afford resin **3**. This resin was swelled in CH_2Cl_2 (10 ml) and treated with TFA (1 ml). The mixture was stirred for 4 h at room temperature, and the resin was collected by filtration. The filtrate was transferred to a separatory funnel and washed successively with 5% $NaHCO_3$, 5% HCl. The aqueous layer was extracted with ether and the combined extracts dried and evaporated to give the corresponding ketones.
9. General procedure for the solid-phase synthesis of aldehydes: To 10 ml of DCM saturated with dry HBr was added the resin **3**. The mixture was stirred at room temperature for 4 h, filtered and washed with DCM, Et_2O to furnish a pale yellow resin **6** (1.11–1.13 mmol Br/g), which exhibited a strong absorption at 630 cm^{-1} (C-Br). The resin **6** was pre-swollen in THF overnight, anhydrous DMSO (1 ml) was added and the mixture was stirred for 1 h. The recovered resin, as deep red beads, was collected by filtration, the filtrate was extracted with ether, the organic layer was washed with water and the combined extracts were dried and evaporated to give the desired aldehydes.