Preparation of Polystyrene-Supported α -Seleno Acetate and Application to Solid-Phase Synthesis of β -Keto Esters

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Abstract: A novel polystyrene-supported α -seleno acetate has been developed. This novel resin was treated with LDA to produce a selenium-stabilized carbanion, which reacted with aldehydes, followed by selenoxide *syn*-elimination to give β -keto esters.

Key words: solid-phase synthesis, α -seleno acetate, selenoxide *syn*-elimination, β -keto esters, polymer reagent

Solid-phase organic synthesis (SPOS) plays an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where the potential has emerged as a result of the possibility of automation.¹

On the other hand, over the past 30 years, organoselenium reagents have been increasingly utilized in highly selective organic reaction, which are especially useful for the construction of complex molecules.² A selenium-stabilized carbanion has played an important role in organic synthesis because of its easy availability and particularly good nucleophile, which allows the formation of new functionalized carbon–carbon bonds when it is used to react with compounds bearing an electrophilic carbon atom.³ However, organic selenium reagents always have a foul smell and are quite toxic, which is often problematic in organic synthesis. Although polymers with selenium functionalities have been known for a long time,⁴ there remains high interest in this kind of solid-phase organic chemistry.⁵

With the continuing evolution of solid-phase organic synthesis (SPOS) comes a growing appreciation for the importance of linker technology, which ideally must accommodate a wide variety of synthetic transformations and yet allow for ready product cleavage in the final solidphase transformation. It might be argued that selenoxide *syn*-elimination provided the principal impetus for the development of SPOS containing selenium moiety.

Our research group has been interested in the application of organoselenium reagents in the solid-phase organic synthesis for many years.⁶ Now, we wish to report the preparation of polystyrene-supported α -seleno acetate and its application for synthesis of β -keto esters. A distinct

SYNLETT 2006, No. 10, pp 1547–1548 Advanced online publication: 12.06.2006 DOI: 10.1055/s-2006-941589; Art ID: W04806ST © Georg Thieme Verlag Stuttgart · New York advantage of the novel polymer reagent is the convenience of handling and odorless nature as compared with the nonpolymer-supported reagents. The preparation of the polystyrene-supported α -seleno acetate is described in Scheme 1.





Following our published protocol⁶ and those of the others,⁵ polystyrene-supported selenenyl bromide (**1**) was prepared with a loading of 1.71 mmol/g (Br) as determined by elemental analysis. Resin **1** reacted with sodium borohydride to give resin **2**, which was treated with ethyl bromoacetate in THF–DMF at room temperature to afford resin **3** (1.64 mmol/g).^{7,8}

Krief and co-workers reported⁹ that α -seleno carbanions obtained according to Sharpless (LDA, THF, -78 °C) react at this temperature with aldehydes producing β -hydroxy selenides in high yield. We examined the same reaction by the resin **3** (Scheme 2). Thus the resin **3** reacted with LDA at -78 °C for 30 minutes, then aldehyde was added. After stirring at -78 °C for another 30 minutes, the mixture was warmed to room temperature within two hours, and then the mixture was filtered. The obtained resin **4** could be converted to β -keto ester by hydrogen peroxide in good yield.¹⁰ The results are shown in Table 1.



Scheme 2

Table 1 Solid-Phase Synthesis of β-Keto Esters

Products	R	Yield (%) ^a	Purity (%) ^b	Ratio of keto /enol ^b
5a	H ₃ CO	78	>90	15:1
5b		80	>90	15:1
5c	0 ₂ N-	87	>95	1:1
5d	$\overline{}$	82	>95	1.6:1
5e	H ₃ C-	81	>90	7.5:1
5f	CI-	86	>95	3.7:1
5g		77	>85	1.6:1
5h	CH2-	64	>80	13:1
5i	(CH ₃) ₂ CHCH ₂ -	56	>85	10:1

^a Yields of products based on the loading of the resin and the products were identified by ¹H NMR, MS, FT-IR spectra.

^b Determined by ¹H NMR (400 MHz).

In conclusion, we have developed a novel polystyrenesupported α -seleno acetate reagent, which were readily prepared from polystyrene-supported selenenyl bromide. This novel resin was treated with LDA to produce a selenium-stabilized carbanion, which reacted with aldehydes, followed by oxidative selenoxide *syn*-elimination to give β -keto esters.

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- (7) **Preparation of Polystyrene-Supported a-Seleno Acetate.** Under a nitrogen atmosphere, resin **1** (2 g; elemental analysis Br, 1.71 mmol/g) was swelled in THF (20 mL) overnight. The mixture added NaBH₄ (10 mmol) stirred at r.t. for 0.5 h and added 2 mL DMF. After 15 h, ethyl bromoacetate (15 mmol) was added and the resulting mixture stirred at r.t. for 12 h. The resin **3** was collected on a filter and washed alternately with THF (2 × 15 mL), H₂O (4×20 mL), EtOH (2 × 15 mL), MeOH (15 mL), THF (2 × 15 mL), CH₂Cl₂ (2 × 15 mL), and dried under vacuum. Resin **3** (1.64 mmol/g): IR (KBr): 3058, 3024, 2922, 1730, 1600, 1587, 1568, 1492, 1452, 1365, 1258, 1104, 1028, 758, 698, 540 cm⁻¹.
- (8) Determined by acid–base titration to be 1.64 mmol/g (COOH). For analytical purposes, the resin of α -seleno acetic acid was prepared by reaction of resin **3** (1 g) with LiOH (1.5 mol/L, 3 mL) in THF (15 mL). After stirred at 35 °C overnight, the resin was washed successively with H₂O, 10% HCl, H₂O, THF and CH₂Cl₂. IR (KBr): 3058, 3024, 2922, 1700, 1600, 1588, 1568, 1492, 1452, 1285, 1106, 758, 698, 541 cm⁻¹.
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- (10) **Typical Procedure for the Synthesis of β-Keto Ester.** Under a nitrogen atmosphere, the resin 3(0.5 g) was suspended in THF (15 mL) at -78 °C and LDA (1 mmol) was added with stirring. The mixture was stirred 0.5 h at -78 °C, then benzaldehyde (1.5 mmol) was added. After stirring at -78 °C for 0.5 h, the mixture was warmed to r.t. in 2 h. Then, the mixture was filtered. The resin 4d was collected by filtration and washed with THF (2×10 mL), MeOH (2×10 mL), CHCl₃ (2×10 mL) and THF (2×10 mL). The washed resin 4d was suspended in THF (15 mL). To the mixture was added 30% H₂O₂ (2 mL) and followed by stirring for 2 h at r.t. The mixture was filtered and the resin was washed with $CHCl_3$ (3 × 15 mL). The filtrate was washed with H_2O (2 × 30 mL), dried over MgSO₄, and evaporated to dryness under vacuum to afford 130 mg (82%) of almost pure ethyl benzoylacetate.