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Facile Solid-Phase Synthesis of Aliphatic Aldehydes Using Novel Polymer-Supported Phenylselenomethyltrimethylsilane

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Abstract: Treatment of a novel polymer-supported phenylselenomethyltrimethylsilane reagent with LDA followed by alkylation and oxidative deselenation efficiently afforded aliphatic aldehydes in moderate to good yields with excellent purities.

Keywords: Aliphatic aldehyde, polystyrene-supported phenylselenomethyltrimethylsilane, solid-phase organic synthesis

Solid-phase methodology has been rapidly and extensively applied to preparation of small organic molecules in recent years. Polymer-supported reagents have attracted growing interest because they can provide attractive and practical methods for combinatorial chemistry and solid-phase synthesis.[1] Synthesis on a polymer support shows a number of advantages as compared to solution chemistry. The most salient one is the possibility to apply excesses of reagents and remove them without using time-consuming separation techniques. Aldehydes are very useful materials and intermediates in organic synthesis. Transformation of organic halides to the corresponding aldehydes is one of important procedures for the synthesis of aldehydes,[2]

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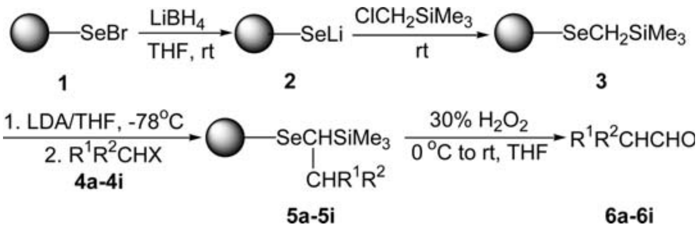

Scheme 1.

among them the oxidation of 1-trimethylsilyl-1-phenylselenoalkane.[3] However, organic selenium reagents are highly malodorous, generally unpleasant, and difficult to handle, especially because of their toxicity. Recently, several groups have developed organoselenium resins as convenient linkers.[4] The use of the selenium reagents immobilized on polymer resin has provided significant advantages, including decreased volatility and simplification of product workup. In continuation of our interest in solid-phase organoselenium chemistry,[5] we herein report a facile synthetic approach to aliphatic aldehydes from novel polystyrene-supported phenylselenomethyltrimethylsilane **3** (Scheme 1).

The resin **3** was prepared conveniently in a nearly quantitative yield by the reaction of cross-linked (1%) polystyrene-supported lithium selenide **2**[4a] with chloromethyltrimethylsilane. The FT-IR spectrum of resin **3** containing 1.19 mmol of Si/g (by elemental analysis) exhibited a characteristic Si-C absorption at 1250 cm^{-1}. Resin **3** appeared to be quite stable in the air at ambient temperature for a long time without diminution of capacity or the liberation of disagreeable odors.

As illustrated, reaction of the lithio derivative of resin **3** with primary alkyl halides **4a–4 h** furnished the α-phenylselenoalkyltrimethylsilane resin (**5a–5 h**), which could not be reliably analyzed with FT-IR. Hence we next carried out a cleavage reaction directly after washing the resin **5** using solvents. Treatment of resin **5** with 30% hydrogen peroxide at 0°C and then at room temperature afforded the corresponding aliphatic aldehydes (**6a–6 h**) in good yields (77–88%) and with excellent purities of crude materials (94–97%). The residual resin, polystyrene-supported phenylseleninic acid, was obtained as a by-product whose infrared data was identical to the previously reported data[6] and which showed no residual Si-C absorption, which indicated the oxidative cleavage was complete. The results of a representative series are summarized in Table 1. However, when secondary halides such as 2-bromoheptane was used, the aldehyde (**6i**) formed with only moderate yield under similar conditions (entry 9, Table 1), perhaps owing to the elimination reaction of 2-bromoheptane (**4i**). Furthermore, when using tertiary halides such as *t*-butyl chloride, the corresponding aldehydes were not obtained.

Table 1. Yields and purities of aliphatic aldehydes (**6a–6i**)

Entry	R^1	R2	X (**4**)	Product	Yield[a] (%)	Purity[b] (%)
1	C_6H_5	H	Cl (**4a**)	**6a**	80	95
2	p-$CH_3C_6H_4$	H	Br (**4b**)	**6b**	81	95
3	p-$CH_3OC_6H_4$	H	Br (**4c**)	**6c**	84	95
4	p-ClC_6H_4	H	Br (**4d**)	**6d**	78	96
5	p-$NO_2C_6H_4$	H	Br (**4e**)	**6e**	78	94
6	$CH_3(CH_2)_2$	H	Br (**4f**)	**6f**	86	97
7	$CH_3(CH_2)_4$	H	I (**4g**)	**6g**	88	96
8	Cyclohexyl	H	Br (**4h**)	**6h**	77	94
9	$CH_3(CH_2)_4$	CH_3	Br (**4i**)	**6i**	60	94

[a] Yields were based on the functional loading of resin **3**.
[b] Purities of crude products were determined by HPLC.

In conclusion, we have developed a facile methodology for the solid-phase synthesis of aliphatic aldehydes in moderate to good yields and with excellent purities based on a polymeric selenium reagent. Although an excess amount of reagents is required, simple workup procedures take the place of the time-consuming isolation and purification steps in the corresponding solution-phase synthesis.

EXPERIMENTAL

Melting points were not corrected. ^1H NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer in $CDCl_3$ with TMS as internal standard. FT-IR spectra were taken on a Perkin Elmer One instrument. THF was newly distilled from sodium/benzophenone before use. Reagents such as lithium diisopropylamide (LDA), chloromethyltrimethyl silane, and organic halides were obtained from commercial suppliers and used without further purification. Polystyrene (100–200 mesh, cross-linked with 1% divinylbenzene) was used for the preparation of polystyrene-supported selenium bromide according to the procedure described by Nicolaou et al.[4a]

Procedure for the Synthesis of Polymer-Supported Phenylselenomethyltrimethylsilane 3

$NaBH_4$ (3 mmol) was added to polystyrene-supported selenium bromide **1** (1.0 g, 1.20 mmol Br/g; the loading of functional Br was analyzed by elementary analysis) swelled in THF (10 mL) and DMF (2 mL) for 30 min under nitrogen. After 6 h with stirring at room temperature, a solution of chloromethyltrimethylsilane (2 mmol) in 2 mL of THF was added slowly, and the mixture was stirred for 6 h. The resin was collected on a filter and washed successively with H_2O, CH_3OH, and CH_2Cl_2 (2 × 3 mL of each) and then dried under vacuum to afford resin **3** containing 1.19 mmol of Si/g as yellow beads. FT-IR (KBr): 3025, 2921, 1600, 1495, 1450, 1250, 1028, 850, 757, 740, 700, 541 cm^{-1}; anal calcd. Si, 3.33%. Found Si, 3.30%.

General Procedure for the Preparation of Aliphatic Aldehydes 6a–6i

Resin **3** (1.0 mmol) was swelled in THF (10 mL) at room temperature for 30 min. After cooling to $-78°C$, a solution of LDA (0.6 mL, 2.0 M, in hexane) was added under nitrogen, and the mixture was stirred at the same temperature for 60 min. Then a solution of primary or secondary alkyl halide **4a**–**4i** (1.5 mmol) in THF (2 mL) was added dropwise. After 2 h, the reaction mixture was warmed up gradually to room temperature and kept standing for 5 h. After the addition of ether–water (5 mL) to the mixture, the resins **5a**–**5i** were collected on a filter and washed successively with H_2O, THF, and Et_2O (3 × 5 mL of each) and then suspended in THF (10 mL) at 0°C and treated with 0.5 mL (5.3 mmol) of 30% H_2O_2. After stirring for 20 min at 0°C, and then at room temperature for 40 min, the residual resin was collected by filtration and washed with CH_2Cl_2 (4 × 5 mL). The filtrate was washed with water (2 × 30 mL), dried over magnesium sulfate, and concentrated in vacuo, and the crude products **6a**–**6i** were obtained and directly analyzed by ^1H NMR and HPLC without further purification.

Data

Phenylacetaldehyde (**6a**):[7] Colorless oil; ^1H NMR δ 9.75 (t, $J = 1.68$ Hz, 1H), 7.34–7.11 (m, 5H), 3.88 (d, $J = 1.68$ Hz, 2H); IR (film) ν_{max} 3030, 2926, 2722, 1703, 1495, 1451, 1359, 1150, 740, 700 cm^{-1}.

***p*-Methylphenylacetaldehyde** (**6b**):[7] Colorless oil; ^1H NMR δ 9.70 (t, $J = 1.68$ Hz, 1H), 7.22 (d, $J = 7.92$ Hz, 2H), 7.08 (d, $J = 7.92$ Hz, 2H), 3.85 (d, $J = 1.68$ Hz, 2H), 2.20 (s, 3H); IR (film) ν_{max} 3029, 2925, 2721, 1708, 1495, 1452, 1375, 1152, 745, 699 cm^{-1}.

***p*-Methoxyphenylacetaldehyde** (**6c**):[8] Colorless oil; ^1H NMR δ 9.65 (t, $J = 1.67$ Hz, 1H), 7.20 (d, $J = 7.90$ Hz, 2H), 7.04 (d, $J = 7.90$ Hz, 2H), 3.85 (d, $J = 1.67$ Hz, 2H), 3.78 (s, 3H); IR (film) ν_{max} 3032, 2927, 2723, 1710, 1500, 1455, 1378, 1155, 826, 746, 697 cm^{-1}.

***p*-Chlorophenylacetaldehyde** (**6d**):[7] Colorless oil; ^1H NMR δ 9.71 (t, $J = 1.69$ Hz, 1H), δ 7.85 (d, $J = 8.56$ Hz, 2H), 7.32 (d, $J = 8.56$ Hz, 2H), 3.88 (d, $J = 1.69$ Hz, 2H); IR (film) ν_{max} 3030, 2925, 2722, 1705, 1498, 1450, 1150, 745, 701 cm^{-1}.

***p*-Nitrophenylacetaldehyde** (**6e**):[7] Pale yellow solid, mp 83–85°C (lit. 83–85°C); ^{1}H NMR δ 9.81 (t, $J = 1.72$ Hz, 1H), 8.28 (d, $J = 8.92$ Hz, 2H), 7.48 (d, $J = 8.92$ Hz, 2H), 3.90 (d, $J = 1.72$ Hz, 2H); IR (film) ν_{max} 3030, 2925, 2720, 1709, 1517, 1425, 1320, 1110, 820 cm^{-1}.

Pentanal (**6f**):[9] Colorless oil; ^{1}H NMR δ 9.81 (t, $J = 1.82$ Hz, 1H), 2.43–2.39 (m, 2H), 1.63–1.56 (m, 2H), 1.35–1.26 (m, 2H), 0.91 (t, $J = 7.31$ Hz, 3H); IR (film) ν_{max} 2961, 2875, 2720, 1721, 1465, 1391, 1119, 1018 cm^{-1}.

Heptanal (**6 g**):[10] Colorless oil; ^{1}H NMR δ 9.78 (t, $J = 1.90$ Hz, 1H), 2.42–2.40 (m, 2H), 1.66–1.50 (m, 6H), 1.36–1.27 (m, 2H), 0.92 (t, $J = 7.31$ Hz, 3H); IR (film) ν_{max} 2960, 2878, 2721, 1722, 1464, 1390, 1120, 1019 cm^{-1}.

Cyclohexylacetaldehyde (**6 h**):[10] Colorless oil; ^{1}H NMR δ 9.76 (t, $J = 1.87$ Hz, 1H), 2.43–2.39 (dd, $J = 7.28$, 1.87 Hz, 2H), 0.98–1.38 (m, 11H); IR (film) ν_{max} 2958, 2873, 2720, 1725, 1465, 1120, 1015 cm^{-1}.

2-Methylheptanal (**6 g**):[10] Colorless oil; ^{1}H NMR δ 9.57 (d, $J = 1.12$ Hz, 1H), 2.42–2.40 (m, 1H), 1.15–1.50 (m, 6H), 1.36–1.26 (m, 2H), 0.90 (t, $J = 7.32$ Hz, 3H), 1.02 (d, $J = 7.40$ Hz, 3H); IR (film) ν_{max} 2961, 2878, 2722, 1726, 1464, 1391, 1120, 1021 cm^{-1}.

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