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Catalytic transfer hydrogenation reactions of PEG-bound succinyl esters☆

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Abstract—Various substrates bound to polyethylene glycol (PEG) through succinyl ester linkages were cleaved under catalytic transfer hydrogenation conditions. The substrates with unsaturated functions also underwent hydrogenation. The protocol was found to be suitable for substrates having acid and base labile functional groups.

1. Introduction

Combinatorial synthesis is a relatively new paradigm for modern day molecular research.[1] Despite several advantages associated with solid-phase reactions, the heterogeneous nature of the reaction conditions can be a major problem in applications to some classical organic reactions. As alternatives, soluble polymers such as polyethylene glycol (PEG) were developed[2,3] as attractive substitutes to solid-phase synthesis by virtue of their ability to be used under familiar reaction conditions of classical organic chemistry. One such advantage is the possibility of utilizing heterogeneous catalysts, which can be readily separated from the polymer support by simple filtration. Of particular interest in the context of our research would be the cleavage of the product from soluble polymers (PEG). A variety of linkers and numerous cleavage methods[4] for particular linkers have evolved for reactions involving PEG-bound substrates. Important cleavage protocols are, (i) heterogeneous hydrogenolysis employing Raney nickel or $NaBH_4$, reductive cleavage via desulfurization using Na–Hg/Na_2HPO_4; (ii) saponification/base catalyzed alcoholysis or hydrolysis with dilute aqueous NaOH; (iii) nucleophilic cleavage reactions involving KCN/MeOH; (iv) free radical initiated cleavage, viz. thioethers and (v) TFA cleavage through acid-catalyzed hydrolysis. Saponification or nucleophilic cleavage involves bases and neither is suitable for base-sensitive substrates. TFA cleavage methods are not suitable for substrates bearing acid-sensitive functions. Hydrogenolysis methods often involve heterogeneous catalysts in the presence of molecular hydrogen.

Even though several heterogeneous reactions including the hydrogenolysis of PEG-bound substrates have been reported, to our knowledge there has been no report on the application of catalytic transfer hydrogenation reactions (CTH) to PEG-bound substrates. Arising from our continued interest in the development of new methodologies for combinatorial synthesis,[5] we report herein a new cleavage protocol for PEG-bound substrates under catalytic transfer hydrogenation conditions.

Several substrates with –OH functions were anchored to PEG through succinyl ester linkages and subjected to catalytic transfer hydrogenation. The cleavage was effected by heating the PEG-bound substrates to reflux in methanol with 10% Pd/C in the presence of ammonium formate as hydrogen source. The cleaved products were isolated from the solvent after precipitation of PEG by addition of diethyl ether. Unsaturated substrates underwent partial or complete hydrogenation, for example, compounds with a double bond or keto functions were transformed into alkanes and alcohols. The cleavage was found to be general for various

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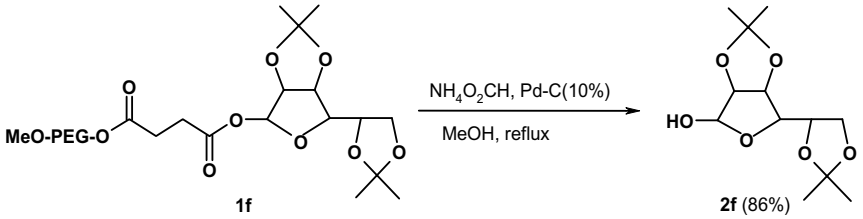
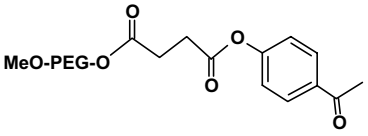
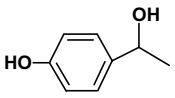
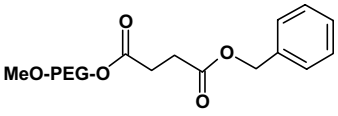
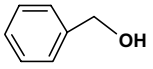
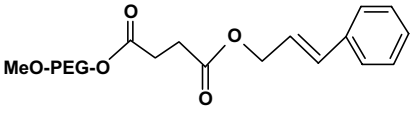
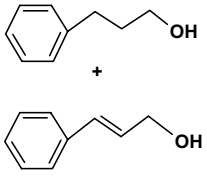
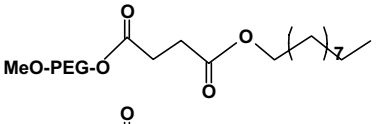
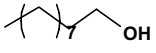
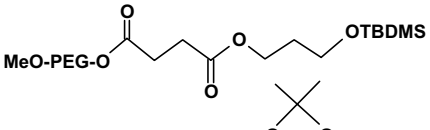
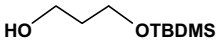
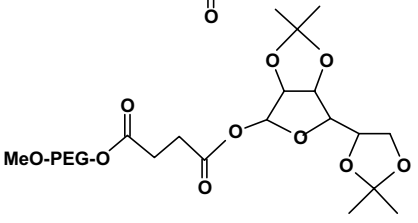
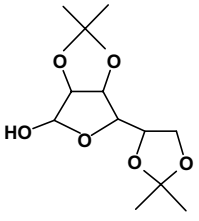
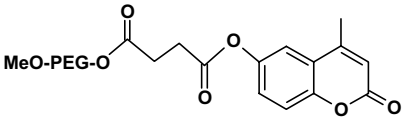
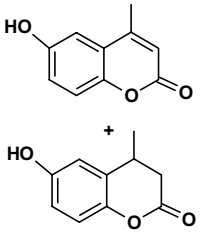


Scheme 1.

PEG-bound substrates such as phenols, saturated alcohols, benzylic and allylic alcohols and protected sugars. Cleavage was found to be nearly quantitative as determined by GC analysis of the crude residue obtained after hydrolysis with 2 N NaOH and this was confirmed by IR and ^{1}H NMR analysis of the PEG obtained during post cleavage work-up. The protocol was found to be suitable for the base-sensitive substrate, 6-hydroxycoumarin, which was found to retain its lactone structure (entry g) but showed partial reduction of the

Table 1. Catalytic transfer hydrogenation of PEG-bound succinyl esters

Entry	Substrate (**1**)	Product (**2**)[a]	Time (h)	Yield (%)[b]
a			8	78
b			7.5	81
c			7	32 57
d			8	84
e			8.5	80
f			8	86
g			12	64 22

[a] The structures of all the products after CTH were determined by ^{1}H NMR and mass spectroscopy and also by comparison with authentic compounds.

[b] Yields based on GC analysis of the crude product obtained after the hydrogen transfer reaction.

double bond. The method is also applicable to acid-sensitive substrates, for example, PEG-bound mannose diacetonide was released in good yields under the CTH conditions without deterioration of its molecular structure (Scheme 1). In conclusion, we have presented in this paper a new cleavage strategy for various PEG-bound succinyl esters employing catalytic transfer hydrogenation. The procedure is suitable for both base- and acid-sensitive substrates and hence may find application as an alternative cleavage protocol for PEG-bound esters (Table 1).

2. Experimental

2.1. Polymer-supported succinyl ester; general procedure

PEG-succinate was prepared by refluxing PEG_{5000} (2 g) with succinic anhydride (0.4 g, 4.0 mmol) in the presence of diisopropylethylamine (DIEA, 1 mL) in dichloromethane (15 mL) for 24 h. After completion of the reaction the solvent was evaporated to reduce the volume to one third. The PEG-supported succinyl ester was precipitated by addition of an excess volume of chilled diethyl ether (150 mL). Filtration and washing with diethyl ether (50 mL) followed by drying under vacuum afforded (1.92 g, 95%) of the product as an off white solid.

2.2. Condensation of polymer-supported succinyl ester with mannose diacetonide general procedure 1f

Mannose diacetonide (1.04 g, 4.0 mmol), dicyclohexylcarbodimide (DCC, 2 g, 9.8 mmol) and a catalytic amount of dimethylaminopyridine (DMAP, 5 mg) were added to the PEG-supported succinyl ester (1.9 g) in dry dichloromethane (25 mL) and the resulting mixture stirred at rt for 24 h under nitrogen. Excess DCC and dicyclohexyl urea formed during the course of reaction were removed by filtration. The filtrate was then concentrated in vacuo. Polymer-supported PEG was precipitated by addition of chilled diethyl ether (200 mL), then filtered and washed thoroughly with excess diethyl ether and dried in vacuum to afford the product as a white solid (1.8 g, 91%).[6]

2.3. Catalytic transfer hydrogenation of PEG-bound substrates; typical procedure

Polymer-supported diacetonide (**1f**, 1.6 g), ammonium formate (1 g, 16 mmol) and a catalytic amount (5% w/w) of Pd/C (10%) were suspended in dry methanol (20 mL). The reaction mixture was heated to reflux for 8 h under nitrogen. The Pd/C was filtered off and the filtrate was evaporated to afford a residue to which dichloromethane (20 mL) was added to precipitate ammonium formate, which was then filtered off. The filtrate was concentrated to one third of its original volume and cleaved PEG was precipitated by the addition of chilled diethyl ether (200 mL). The PEG was washed with diethyl ether (75 mL) and the combined ether extracts were concentrated in vacuo to afford a crude product, which was purified by chromatography (silica gel >200 mesh, elution, EtOAc/hexane gradient; *n*-hexane to 2:1 *n*-hexane–EtOAc) to afford pure mannose diacetonide **2f** (0.065 g, 85%).

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6. PEG-supported mannose diacetonide (**1f**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 2.73 (m, 4H, –$OCCH_2CH_2CO$–), 3.46–3.81 (m, PEG), 3.95–4.10 (m, 2H), 4.25 (t, J = 4.2 Hz, 2H, –PEG–OCH_2CH_2OCO), 4.30 (m, 2H), 4.60 (d, 1H, J = 7.4 Hz), 4.80 (t, 1H, J = 7.4 Hz), 6.10 (d, 1H, J = 3.4 Hz).