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A New Variant of the Baylis-Hillman Reaction
for Solid Phase Organic Synthesis.

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Abstract:A new variant of the Baylis-Hillman reaction based on lithium phenylselenide is adapted to Solid Phase Organic Synthesis (SPOS). Scope and limitations are studied using four polymer bound aldehydes.

Keywords: Solid phase synthesis, Baylis-Hillman reactions.

During our work towards the total synthesis of mniopetals[1] and kuehneromycins[2] we developed a new variant of the Baylis-Hillman reaction.[3, 4] Here we wish to report our results concerning the transformation of this reaction to SPOS.

In our synthesis of a key intermediate for the mniopetals and kuehneromycins we developed a new variant of the Baylis-Hillman reaction based on lithium phenylselenide as nucleophile since standard conditions of the Baylis-Hillman reaction with DABCO as nucleophile do not work with b -substituted acrylic acid derivatives, such as Feringa´s butenolide **1**.[5] The optimum reaction conditions in solution were concentrations of the reagents of 0.1 mol/l with an excess of aldehyde (1.5 eq.) (Scheme 1).
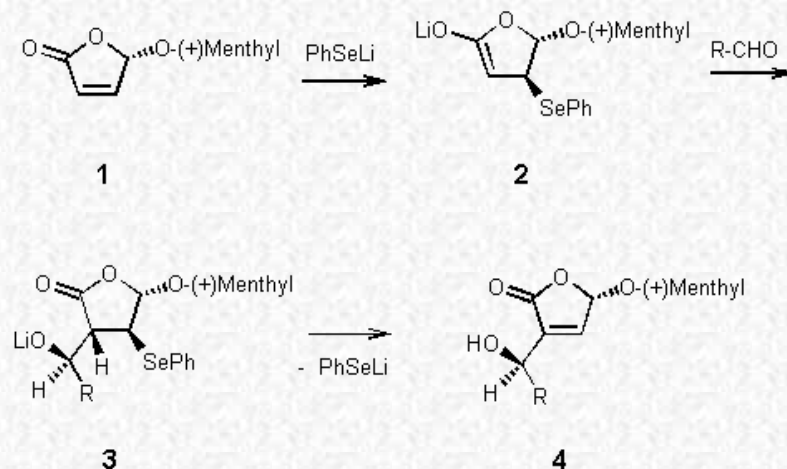
Scheme 1. Baylis-Hillman reaction with PhSeLi as nucleophile.

To adapt this PhSeLi induced Baylis-Hillman reaction to SPOS, two problems had to be solved. First, using excess of polymer bound aldehyde with respect to Feringa´s butenolide is impractical, since this would result in incomplete reaction of the polymer bound aldehyde. Second, to fully cover the resin, more solvent than in homogenous phase has to be used, which leads to lower concentrations of reagents and slows down the reaction dramatically. This is a general problem of SPOS, which usually is solved by using an

excess of reagents. Here, we used ten equivalents of PhSeLi with respect to polymer bound aldehyde and 1.5 equivalents of Feringa´s butenolide **1** or five equivalents of PhSeLi and 2.5 eq. of **1** and thus could completely couple **1** with **5** to trienolide **6** in reasonable reaction time (Scheme 2).[6, 7]
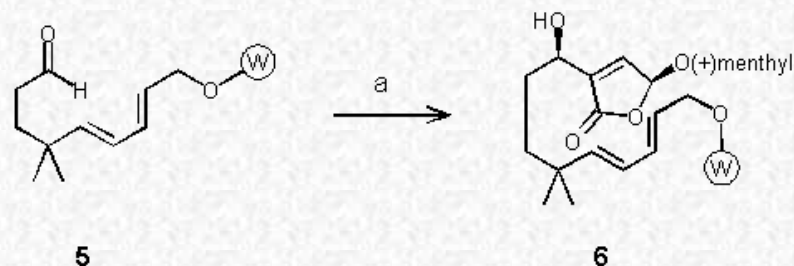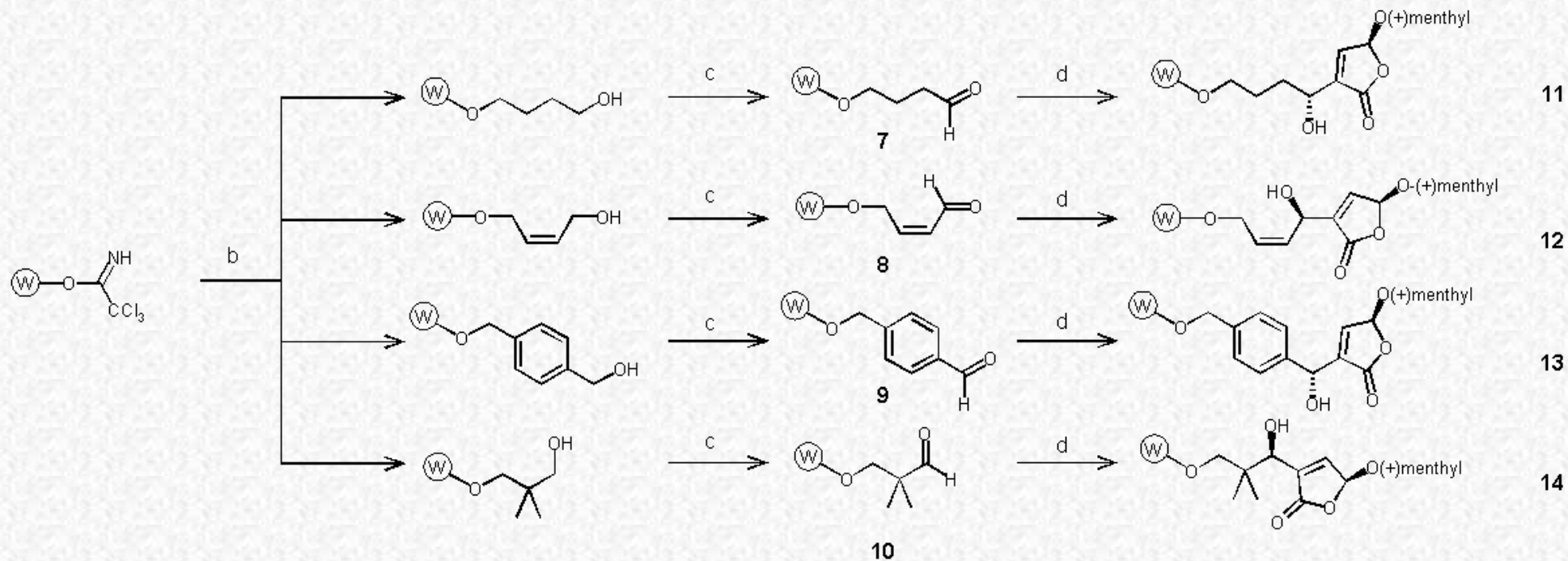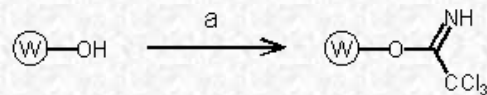

a) PhSeLi (10 eq.), **1** (1.5 eq.), -60 °C to -30 °C, over night (alternatively PhSeLi (5 eq.), **1** (2.5 eq.), -60 °C to -30 °C, over night).

Scheme 2. PhSeLi induced Baylis-Hillman reaction of **1** and **5**.

6 is characterized by ^{13}C gel phase NMR spectroscopy. The chemical shifts of the signals in the ^{13}C-NMR spectrum of **6** are identical to those of a trienolide analogous to **6** synthesized in solution.

This indicates that the PhSeLi variant of the Baylis-Hillman reaction on solid phase is highly diastereoselective (as already found for the corresponding reaction in homogenous phase[3]). **6** is the starting material for an intramolecular Diels-Alder reaction after *ins situ* oxidation of the secondary alcohol to the corresponding ketone.[8]

To study scope and limitations of the new variant of the Baylis-Hillman reaction in SPOS, we synthesized the structurally diverse aldehydes **7**, **8**, **9** and **10** through coupling of *in situ* prepared Wang trichloroacetimidate[9] with the corresponding diols and subsequent oxidation with o-iodoxybenzoic acid (IBX).[10, 11] These aldehydes were transformed into the polymer bound butenolides **11**, **12**, **13** and **14** using the reaction conditions[6] developed for the synthesis of **6** (Scheme 3). The butenolides **11**,[12] **13**[13] and **14** could be cleaved from the Wang resin with DDQ at room temperature during 40 min. and were characterized by NMR spectroscopy. Cleavage of the butenolide **12** from Wang resin with DDQ resulted in formation of a hydroxy aldehyde, which probably reacts with itself forming a complex mixture of products which have not been further characterized.

a) CCl$_3$CN (1.3 eq.), DBU (0.1 eq.), rt, 1h; b) HO-R-OH (3 eq.), BF$_3$·Et$_2$O (0.1 eq.) 0 °C to rt, 1h; c) IBX (3 eq.), rt, 2-5 h; d) PhSeLi (10 eq.), **1** (1.5 eq.), -60 °C to -30 °C, over night; d′) PhSeLi (10 eq.), **1** (1.5 eq.), -30 °C, 72 h.

Scheme 3. PhSeLi induced Baylis-Hillman reaction of structurally diverse aldehydes.

Cleavage of the polymer bound substances with DDQ was performed under standard conditions and after filtration of insoluble material, separation of the organic layer and drying with MgSO$_4$ resulted in crude products with high purity (> 95%, estimated by ^{1}H-NMR spectroscopy) but only low yields of 30-35%, based on the capacity of the starting Wang resin.

Acknowledgement

References

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Baylis-Hillman reactions with resin bound acrylic acids under classic conditions using DABCO as nucleophile have been reported by Prien, O.; Rölfing, K.; Thiel, M.; Künzer, H. *Synlett* **1997**, 325-326 and Richter, H.; Walk, T.; Höltzel, A.; Jung, G. *J. Org. Chem.* **1999**, *64*, 1362.

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(6) A typical procedure for the PhSeLi induced Baylis-Hillman reaction in SPOS is as follows:
6: 0.81 ml of 1.6 M *n*-BuLi (1.3 mmol) in hexanes is added at
–20 °C under N_2 to 406 mg diphenyl diselenide (1.3 mmol), dissolved in 1 ml of anhyd. THF. This solution is cooled to
–60 °C and added in one portion to a mixture of 200 mg resin **5** (loading ca. 260 mmol) and 155 mg Feringa´s butenolide **1** (650 mmol) at –60 °C. The resulting suspension is degassed (vacuum) and warmed to – 30 °C over night with slow stirring. Then, the resin is filtered, washed with H_2O, acetone, THF, CH_2Cl_2 and diethyl ether and dried in vacuo. ^{13}C gel pase NMR (90.6 MHz, $CDCl_3$): 144.4; 143.2; 140.0; 133.5; 127.6; 126.2; 99.1; 79.1; 70.1; 67.0; 47.8; 35.8; 34.3; 31.5; 27.0; 25.5; 23.3; 22.3; 20.9; 16.0. The signals of the quarternary carbon atoms were too small to be observed. Additionally, some signals are superimposed by the signals of polystyrene-Wang resin.

(7) Often, reaction conditions in SPOS have to be developed by trial and error, if no direct reaction monitoring (eg TLC, GC, HPLC, etc.) is possible. In this particular case reported here, the reactions were followed by means of adding a tiny amount of a similar soluble aldehyde to the reaction mixture (octanal, citral, benzaldehyde, pivalin aldehyde). In slow reactions, where diffusion plays a subordinate part, the soluble aldehydes should react as fast as the immobilized ones. So it is possible to determine the reaction progress by so called *indirect reaction monitoring* by simple methods like TLC, GC etc.

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(11) General procedure for the oxidation of polymer bound alcohols to aldehydes with IBX: 200 mg of polymer bound alcohol (loading ca. 260 mmol) and 182 mg of IBX (650 mmol) are suspended in 1 ml DMSO. The mixture is degassed (vacuum) and stirred slowly until most of the IBX is dissloved. After addition of 1 ml of THF for better swelling, the mixture is stirred for 2-5 h at room temperature. The resin is filtered and washed extensively with DMSO, H_2O, acetone, THF and diethyl ether. After drying in vacuo the resin is characterized by ^{13}C gel phase NMR spectroscopy.

(12) **11** (cleaved from Wang resin): ^{1}H-NMR (360 MHz, $CDCl_3$): 6.97 (d, 1.3Hz, 1H); 6.00 (s, 1H); 4.55 (m, 1H); 3.73 (m, 2H); 3.64 (td, 10.4 Hz, 4.5 Hz, 1H); 2.20-1.93 (m, 2H); 1.85-1.15 (m, 8H); 0.95 (d, 6.5Hz, 3H); 0.88 (d, 6.5 Hz, 3H); 0.80 (d, 7.1 Hz, 3H); 1.15-0.7 (m, 3H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 170.6; 143.5; 140.0; 99.3; 79.3; 66.7; 62.7; 47.7; 40.4; 34.2; 32.8; 31.5; 28.4; 25.4; 23.2; 22.2; 20.8; 15.8.

(13) **13**: ^{13}C gel phase NMR (90.6 MHz, $CDCl_3$): 143.8; 127.8; 126.7; 99.3; 79.1; 68.8; 47.7; 34.2; 31.4; 25.4; 23.2; 22.2; 20.9; 15.9; some signals are superimposed by signals of polystyrene-Wang resin.