Report

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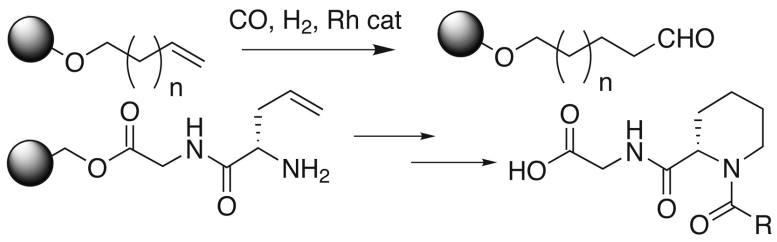
J. Comb. Chem., **2003**, 5 (3), 198-200• DOI: 10.1021/cc020055s • Publication Date (Web): 01 April 2003



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Reports

Hydroformylation of Terminal Alkenes Supported on Solid Phase: Synthetic Tool for Combinatorial Chemistry

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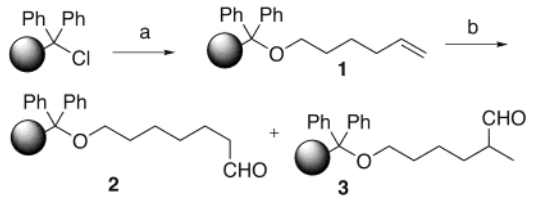
Received July 22, 2002

The combinatorial approach to organic synthesis has changed the way of thinking of synthetic transformations in the past decade. Old and new reactions have been (re)-investigated, looking to the efficacy and possibility of automation with the objective of producing collections of individual compounds to submit to HTS (high-throughput-screening).[1] Hundreds of "classical" organic transformations have been adapted to solid phase with excellent results in terms of efficacy and variety of structures prepared, as documented by several reviews on the argument.[2] Notwithstanding these results, there is still the need to introduce new reactions into the arsenal of solid-phase organic transformations to increase the potential molecular diversity and to allow the synthesis on solid phase of additional classes of molecules.

On the other hand, hydroformylation of alkenes is a well-established synthetic tool for the preparation of aldehydes, their derivatives, and other products obtainable from them.[3] Despite this potential interest in combinatorial chemistry, hydroformylation of alkenes supported on the most common resins in use, as PS-DVB (polystyrene/divinylbenzene) microporous beads, has never been attempted.[4]

Following our interest in development of chemical reactivity on solid phase,[5] we were intrigued by the possibility of performing hydroformylation on solid-supported alkenes. To explore the reaction conditions, compound **1** was prepared loading 5-hexen-1-ol on a PS-DVB resin with a trityl linker. In the first experiments, beads of **1** were placed in a classical glass vial for hydroformylation and mixed with a solution of $Rh(CO)_2(acac)$ in toluene. The solution was submitted to pressurized syngas ($CO/H_2 = 1$) from 20 to 100 bar and temperatures from 50 to 100 °C. The transformation was monitored on beads, using a colorimetric test for aldehydes[6] or FT-IR, looking to the carbonyl stretching at 1750−1715 cm^{-1}. Under those conditions, hydroformylation did not occur. Upon increasing the temperature to 140 °C, a partial transformation was observed at FT-IR. A GC/mass analysis of the reaction products, after cleavage, showed <20% conversion.

Scheme 1



(A) 5-Hexen-1-ol (20 equiv), Py, 50 °C, 48 h. (B) Catalyst, CO/H_2 1:1, 20 bar 40 °C, 48 h.

The previous experiments were carried out without agitation because the presence of a magnetic bar in the vial could damage the gel-phase beads.[7] The absence of agitation could prevent the syngas from dissolving in toluene and reaching the solid-supported substrate. We designed a modified vial to allow stirring of the solution during hydroformylation without damaging the resin. The beads were placed in a basket with a sintered glass on the bottom. The basket was placed inside the vial for hydroformylation, and the level of the toluene solution containing the catalysts was regulated to cover the beads.

A magnetic stirring bar was placed on the bottom of the vial to allow the mixing of the solution. The vial was inserted in the stainless steel autoclave and the hydroformylation was carried out. At the end, the basket was removed, the beads were washed, and the products were analyzed.[8] With this apparatus (see Supporting Information), products **2** and **3** were obtained in high yields (from 85 to 99%). The presence of the aldehyde was monitored on the beads using the colorimetric tests and FT-IR. The products were then cleaved and analyzed by GC/mass and ^1H NMR.

Hydroformylation with $Rh(CO)_2(acac)$ gave a mixture of the linear and branched aldehydes **2** and **3** in a 1:1 ratio. The ratio was increased to 8.5:1.5 using the Wilkinson catalysts together with the ligand Xantphos.[9] This catalytic system was employed for the hydroformylation of different resin-linked alkenes (compounds **4**−**8** in Scheme 2). The identities of products **2**, **3**, and **9**−**13** were determined by comparison of the MS and NMR spectra with authentic samples.

All of the substrates were hydroformylated in a relatively short time, with very good yields and good regioselectivity that was particularly high in the hydroformylation of acrylates

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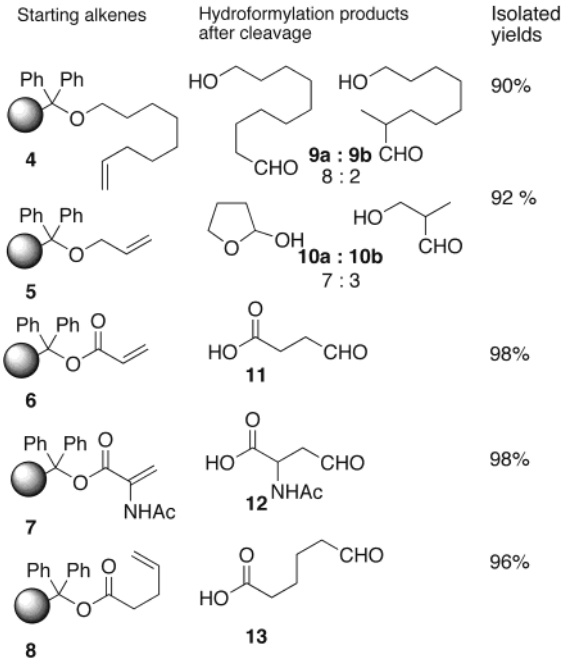
10.1021/cc020055s CCC: $25.00
Published on Web 04/01/2003

Scheme 2



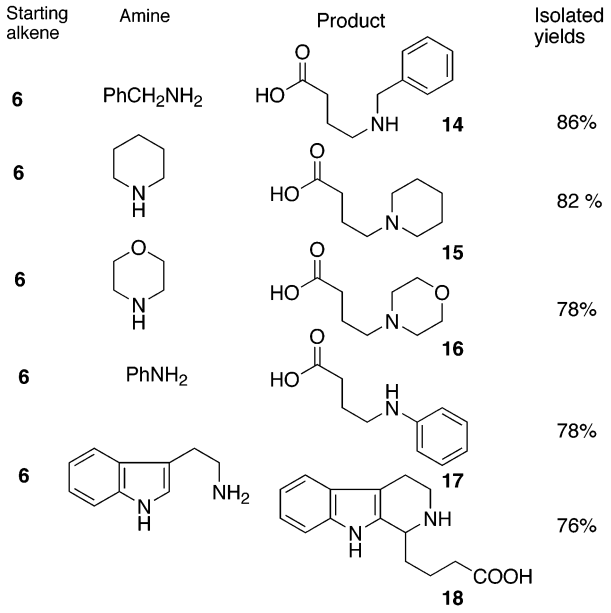
6 and **7** or the alkenyl ester **8**.[10] Moreover, the same solution containing the catalysts was reused several times, maintaining a good level of activity.

Encouraged by these results, we tried to investigate the hydroformylation in a tandem or domino-reaction sequence.[11] The intramolecular hydroformylation reductive amination has been largely employed[12] in the homogeneous phase and could be used for the preparation of libraries of amines on the solid phase. Consequently, hydroformylation was carried out on supported alkene **6** in the presence of different amines and the catalytic system $HRh(CO)(PPh_3)_2$/Xantphos under 20 bar of H_2/CO 1:1 at 40 °C for 48 h. At the end, the resin was recovered, washed several times, and treated with TFA in CH_2Cl_2 to cleave the products from the resin. Compounds **14**−**17** were obtained in good yields, as reported in Scheme 3.

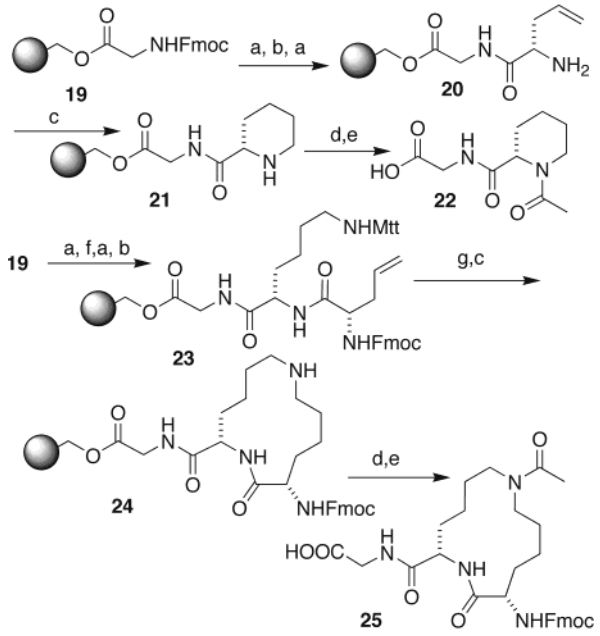
Compound **18** was obtained from hydroformylation reductive amination in the presence of tryptamine and further Pictet−Spengler reaction on the resin.[13] An intramolecular version of the reaction was performed on a peptide containing a terminal alkene. A *N*-Fmoc-Gly loaded on a Wang resin (**19**) was deprotected under standard conditions, coupled with *N*-Fmoc-allylglycine (using DMTMM as the coupling agent;[14] DMF; *N*-methyl morpholine, NMM) and deprotected to give product **18**. The beads were hydroformylated ($HRh(CO)(PPh_3)_2$/Xantphos 1:4, toluene, H_2/CO 1:1, at 20 bar and 40 °C). After 48 h, the Kaiser test was negative and the chloranil test was positive,[15] suggesting that the pipecolic derivative **21** was formed. The product was reacted with Ac_2O and diisopropylamine (DIPEA) in DMF (negative chloranil test), and the cleavage with TFA in CH_2Cl_2 gave compound **22** in 78% yields.

The possibility of carrying out an intramolecular reductive amination in tandem with the hydroformylation on solid phase induced us to explore the opportunity of using this procedure to prepare conformationally constrained macrocyclic peptide derivatives. Cyclic peptides are of great interest

Scheme 3



Scheme 4[a]



[a] (a) 25% Piperidine in DMF, 40 min. (b) *N*-Fmoc-allylglycine (2 equiv), DMTMM (2 equiv), NMM (4 equiv), DMF, 4 h. (c) CO/H_2 1:1, 20 bar 40 °C, $HRh(CO)(PPh_3)_3$/Xantphos 1/4 (0.04 equiv), 48 h. (d) Ac_2O, DIPEA, DMF, 3 h. (e) 50% TFA CH_2Cl_2, Et_3SiH (5 equiv), 2 h. (f) *e*-Mtt-*a*-*N*-Fmoc-Lys-OH (2 equiv), DMTMM (2 equiv), NMM (4 equiv), DMF, 6 h. (g) 1% TFA, CH_2Cl_2, 3 cycles of 2 min.

for their improved biological properties in crossing membranes, surviving reaction by endopeptidases, and binding more selectively to receptors.[16]

Resin **19** was coupled with *e*-Mtt-*a*-*N*-Fmoc-Lys-OH[17] (DMTT, NMM, DMF), followed by Fmoc deprotection and coupling with *N*-Fmoc-allylglycine to give product **23** (Scheme 4). The Mtm group was removed using 1% TFA in CH_2Cl_2 (positive Kaiser test), and the product was hydroformylated under standard conditions to give macrocyclic **24**, as suggested by a positive chloranil test. After acetylation of the NH group with Ac_2O, DIPEA in DMF,

and cleavage with TFA/CH_2Cl_2 1:1, product **24** was isolated in 56% yield after HPLC purification.[18]

In conclusion, we have demonstrated that hydroformylation and tandem hydroformylation−reductive amination can be carried out successfully on terminal alkenes supported on PS-DVB resins with classical trityl or Wang linkers. Application of this technology to the preparation of libraries of small organic molecules and natural product-like compounds is in progress and will be reported in due course.

Acknowledgment. This work was supported in part by CNR (Rome) and in part by MIUR (Rome) within the project PRIN 2001

Supporting Information Available. The figure of the glass apparatus for hydroformylation, characterization of compounds **14**−**18** and experimental preparations for **22** and **25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(18) Compound **22** was characterized by HPLC/ES-MS analysis, which showed the presence of <10% of oligomers with higher molecular weight. Moreover, HPLC and NMR analysis showed the presence of a single diastereoisomer, suggesting that racemization did not occur during the reaction.

CC020055S