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Barbier allylation–Prins reaction of PEG-bound aldehydes—soluble polymer-supported synthesis of 2,4,6-trisubstituted tetrahydropyrans

H. M. Sampath Kumar,[a,b,*] Naveed Ahmed Qazi,[b] Syed Shafi,[b] V. Naveen Kumar,[a] A. D. Krishna[a] and J. S. Yadav[a]

[a]*Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India*
[b]*Regional Research Laboratory, Jammu-Tawi-180 001, India*

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Abstract—PEG-bound aldehydes undergo zinc-mediated Barbier allylation to form homoallylic alcohols, which on further reaction with various aldehydes in the presence of $BF_3{\cdot}Et_2O$ through a Prins cyclization afford 4-hydroxytetrahydropyrans and 4-fluorotetrahydropyrans.

Cross-linked polymer supports are now ubiquitous throughout the fields of combinatorial chemistry, organic synthesis, catalysis and reagents.[1] However, emerging problems associated with the heterogeneous nature of the ensuing chemistry together with the difficulties associated with 'on-bead' spectroscopic characterization prompted the development of soluble polymers as alternative matrices for the production of combinatorial libraries.[2] The lower reactivity of polystyrene-bound substrates, attributed to a pseudo-dilution effect, can be circumvented in the case of soluble polymers, as reactions of soluble polymer-bound substrates and unbound reactant show the same kinetics, with the additional advantage of being able to separate the unbound byproducts and excess reagents by preferential precipitation of PEG in solvents. Moreover, polyethylene glycols are relatively cheaper and are amenable to two-phase reactions as compared to cross-linked polystyrenes.

The Prins reaction involving the acid-catalyzed reaction of olefins with aldehydes is an important carbon–carbon bond forming reaction. The pyran ring forms an important structural feature of many valuable natural products.[3] Pyran derivatives can be obtained by the acid-catalyzed Prins reaction of aldehydes with homoallylic alcohols. As part of our continued interest in the development of protocols for combinatorial chemistry, we report herein the synthesis of substituted tetrahydropyrans through Barbier allylation followed by Prins reaction of PEG-bound aldehydes, which to our knowledge has not been hitherto reported (Scheme 1).

Hydroxy aldehydes such as *m*- and *p*-hydroxybenzaldehydes were anchored to mono methoxy-PEG (Aldrich, average M_n ca. 2000) bound succinic acid half ester, employing carbodiimide coupling followed by the reaction with allyl bromide and zinc metal in dry tetrahydrofuran. The allylation reactions proceeded smoothly to afford the corresponding homoallylic alcohols quantitatively, as revealed by ^1H NMR analysis of the PEG-bound product. The PEG-bound homoallylic alcohol was in turn reacted with excess of various aldehydes in the presence of $BF_3{\cdot}Et_2O$ at ambient temperature under a nitrogen atmosphere. After quenching with water (2 ml) and evaporation, dissolving the residue in dichloromethane and precipitation with ether gave PEG-bound tetrahydropyranol derivatives as major products and fluoro-substituted tetrahydropyrans in minor quantities. The products were cleaved from the polymer by treatment with 2 N NaOH for 2–3 h followed by neutralization and solvent extraction. The structures of the Prins cyclization products

Keywords: PEG; Barbier allylation; Prins cyclization; Tetrahydropyran.
* Corresponding author. Fax: +91 0191 2548607/2573765; e-mail: hmskumar@yahoo.com

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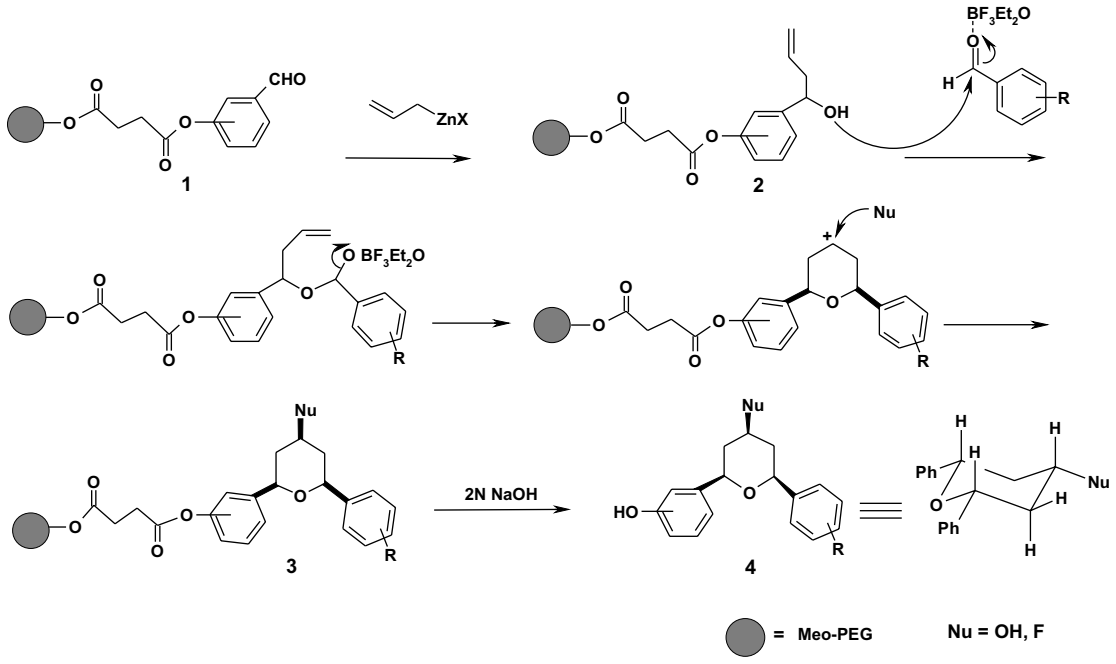
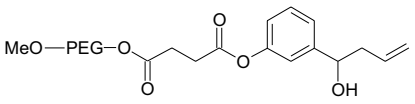
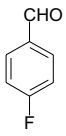
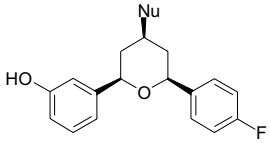
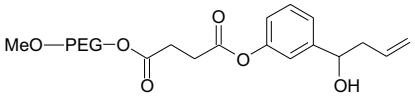
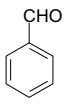
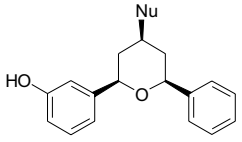
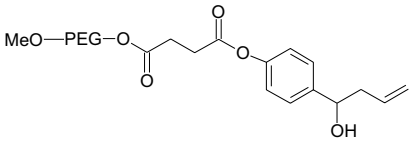
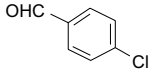
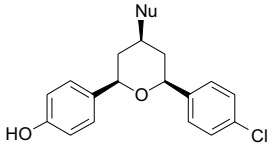
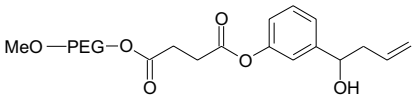
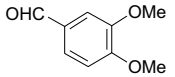
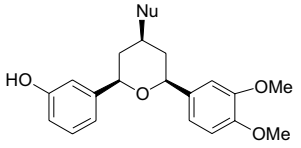
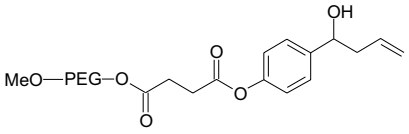
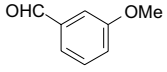
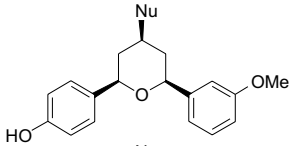
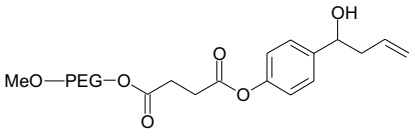
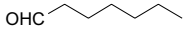
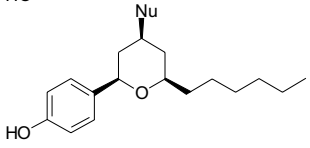


Scheme 1.

Table 1. Combinatorial synthesis of substituted tetrahydropyrans in liquid phase[5]

Entry	PEG-bound allylic alcohol	Aldehyde	Product after cleavage[a]	Yield %[b] (ratio OH/F)
a				65 (81:19)
b				61 (78:22)
c				67 (84:16)
d				82 (80:20)
e				63 (85:15)
f				59 (81:19)

[a] All compounds were characterized by ^{1}H NMR and mass spectroscopy.
[b] Yield and ratio based on the analysis of product mixture obtained after cleavage.

were confirmed by ^{1}H NMR of PEG-bound products as well as by ^{1}H NMR and high-resolution mass spectral analysis of the materials obtained after cleavage. By comparison of the spectroscopic data with the literature reported values,[4] the products were identified as the stereoisomers in which the two phenyl rings and the hydroxyl (or fluoro) are equatorial. As proposed before for the formation of such products in solution phase, the predominant formation of the all-equatorial product can be attributed to a thermodynamic effect. A minor quantity of the corresponding fluoro derivatives formed by the attack of fluoride ion derived from BF_3 was detected again as encountered in the solution phase reaction (Table 1).[3,4]

In conclusion, we have demonstrated here an efficient liquid-phase synthesis of 4-hydroxytetrahydropyrans and 4-fluorotetrahydropyrans through two-step reactions involving zinc-mediated allylation of PEG-bound aldehydes followed by Prins reaction.

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5. Liquid-phase synthesis of 4-hydroxy/fluoro tetrahydropyrans.
Polymer-supported hydroxybenzaldehyde: general procedure—Hydroxy-benzaldehyde (2 mmol), DCC (0.206 g, 1 mmol) and a catalytic amount of DMAP (0.005 g) were added to PEG-supported succinate (1 g, approximately quantitative loading (0.5 mmol/g as determined by IR, NMR analysis)) in dry CH_2Cl_2 (15 ml). The mixture was stirred at rt for 16 h. The precipitated urea was removed by filtration and the filtrate was concentrated to one third of its original volume and diluted with Et_2O (200 ml). The precipitate was collected, washed with Et_2O and dried, affording the polymer-supported hydroxybenzaldehyde.
1a. ^{1}H NMR ($CDCl_3$): δ 2.80 (m, 4H, –OCCH_2CH_2CO–), 3.40 (s, 3H), 3.46–3.81 (m, PEG), 3.95–4.10 (m, 2H), 4.25 (t, $J = 4.7$ Hz, 2H, –PEG–OCH$_2CH_2$OCO), 7.30 (d, $J = 7.3$ Hz, 2H), 7.90 (d, $J = 7.30$ Hz, 2H), 10.00 (s, 1H).
Zinc mediated allylation of PEG-bound aldehydes. Allylzinc reagent was generated by stirring allyl bromide (0.5 g, 4.1 mmol) with freshly activated zinc (0.4 g, 6.2 mmol) in dry THF under nitrogen. Formation of a clear solution on dissolution of zinc indicated the generation of the reagent. Polymer-bound aldehyde (2.0 g, 0.5 mmol loading) dissolved in dry THF (20 ml) was added to the allylzinc reagent in one portion and the mixture was stirred at ambient temperature for 10 h at the end of which, the reaction was quenched by the addition of saturated ammonium chloride solution (2 ml). Work-up involved the evaporation of THF under reduced pressure, followed by dissolution of residue with CH_2Cl_2 (40 ml), separation of undissolved inorganic salts by filtration, concentration of the dichloromethane filtrate followed by precipitation of PEG by dilution with excess of diethyl ether (400 ml), then by filtration.
2a. ^{1}H NMR ($CDCl_3$): δ 2.80 (m, 4H, OCCH_2CH_2CO–), 3.40 (s, 3H), 3.46–3.81 (m, PEG), 3.95–4.10 (m, 2H), 4.25 (t, $J = 4.7$ Hz, 2H, –PEG–OCH$_2CH_2$OCO), 4.75 (t, 1H), 5.20 (m, 2H), 5.8 (m, 1H), 7.10 (d, 2H, $J = 8.6$ Hz), 7.40 (d, 2H, $J = 8.60$ Hz).
Polymer-supported Prins reaction of homoallylic alcohol catalyzed by $BF_3{\cdot}Et_2O$:PEG-bound homoallylic alcohol (1.6 g, 0.5 mmol loading) was dissolved in dry dichloromethane (10 ml). The solution was cooled in ice-bath. *p*-Chlorobenzaldehyde (0.84 g, 6.0 mmol) and $BF_3{\cdot}Et_2O$ (0.30 ml) were added and the resulting clear solution was stirred in ice-bath for 2 h and slowly allowed to attain rt, then stirring was continued for another 15 h. The reaction mass was quenched with water (1 ml) and evaporated to dryness and the residue was dissolved again in CH_2Cl_2 (6.0 ml) and precipitated again by the addition of excess diethyl ether (250 ml) to afford an off-white amorphous solid. ^{1}H NMR analysis of PEG-bound compound clearly revealed the formation of hydroxyl tetrahydropyran through Prins cyclization. Final cleavage was effected by stirring the PEG-bound compound with 2 N NaOH for 3 h, followed by neutralization and extraction with ethyl acetate (2×30 ml) and evaporation affording crude product containing 4-hydroxyl and 4-fluoro-tetrahydropyran. Formation of the product could be ascertained by ^{1}H NMR ($CDCl_3$) of PEG-bound compound and also after cleavage 2 N NaOH and ^{1}H NMR analysis of the products (**4** and **5**) was obtained after work up and chromatography.
3c (mixture of hydroxy and fluoro derivatives). ^{1}H NMR ($CDCl_3$): δ 2.80 (m, –OCCH$_2$CH$_2$CO–), 3.40 (s), 3.46–3.81 (m, PEG), 3.95–4.10 (m), 4.25 (t, $J = 4.7$ Hz, –PEG–OCH$_2CH_2$OCO), 4.50 (d, $J = 11.1$ Hz), 5.10 (d, $J = 10.9$ Hz), 7.1–7.2 (d, $J = 8.4$ Hz), 7.40 (d, $J = 8.7$ Hz), 7.50–7.60 (d, $J = 8.4$ Hz.), 7.70 (d, $J = 8.7$ Hz).
4. 2-(4-Chlorophenyl)-6-(4-hydroxyphenyl)-tetrahydro-4-hydroxy-2-pyran: ^{1}H NMR ($CDCl_3$): δ 1.6 (m, 2H), 2.30 (m, 2H), 4.10 (m, 1H), 4.50 (d, 2H, $J = 11.1$ Hz), 7.00 (d, $J = 8.4$, 2H), 7.30 (d, $J = 8.7$, 2H), 7.50 (d, $J = 8.4$, 2H), 7.70 (d, $J = 8.7$, 2H). HREIMS: 304.7 (calcd for $C_{17}H_{17}ClO_3$, 304.77).
5. 2-(4-Chlorophenyl)-6-(4-hydroxyphenyl)-tetrahydro-4-fluoro-2-pyran: ^{1}H NMR ($CDCl_3$): δ 1.60 (m, 2H), 2.30 (m, 2H), 4.10 (m, 1H), 5.00 (d, 2H, $J = 10.9$ Hz) 7.00 (d, $J = 8.4$, 2H), 7.30 (d, $J = 8.7$, 2H), 7.60 (d, $J = 8.4$, 2H), 7.70 (d, $J = 8.7$, 2H). HREIMS: 306.7 (calcd for $C_{17}H_{16}ClFO_2$, 306.76).