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Ferrier rearrangement for the synthesis of PEG-bound 2,3-unsaturated glycopyranosyl-amino acids☆

Bilal A. Bhat, Syed Shafi, Basant Purnima, Abid Hussain Banday and H. M. Sampath Kumar*

Synthetic Chemistry Section, Regional Research Laboratory, Jammu-Tawi 180 001, India

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Abstract—Amino acid 2,3-unsaturated glycopyranosyls have been prepared by the Ferrier rearrangement of acetyl protected glucals and PEG-bound amino acids in the presence of a catalytic quantity of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at ambient temperature.

Ever since the development of combinatorial chemistry,[1] new protocols adaptable to polymeric matrices have been developed from time to time,[2] to cater for the new challenges associated with polymer-supported synthesis. Cross-linked polymer supports are now ubiquitous throughout the fields of combinatorial chemistry, organic synthesis, catalysis and reagents.[3] However, problems associated with the heterogeneous nature of the ensuing chemistry together with the difficulties associated with 'on-bead' spectroscopic characterization have prompted the development of soluble polymers as alternative matrices for the production of combinatorial libraries.[4] The lower reactivity of polystyrene-bound substrates, attributed to pseudo-dilution effects, can be circumvented in the case of soluble polymer-bound substrates and unbound reactants show the same kinetics, with the additional advantage of being able to separate the unbound by-products and excess reagents by preferential precipitation of PEG in solvents. 2,3-Unsaturated glycosides have received wide attention in recent years, particularly in the synthesis of several biologically active natural products and also as chiral synthons. Aryl and alkyl 2,3-unsaturated glucosides are accessible by acid catalyzed nucleophilic substitution with allylic rearrangement of tri-*O*-acetylglucal, however, it is not that easy to prepare 2,3-unsaturated galactosides by this route. This reaction, often referred to as the 'Ferrier rearrangement'[5] has found wide application and thus continues to be important in the chemistry of the 2,3-unsaturated sugars. The fact that tri-*O*-acetyl glucal[6] can be easily synthesized from glucose, adds to its importance. The Ferrier rearrangement continues to receive wide attention and various glycosidation methodologies that utilize it have been extensively reviewed.[7] In continuation of our interest in the development of novel liquid phase methodologies[8] for combinatorial synthesis, herein we report a liquid phase synthesis of 2,3-unsaturated glycosidic amino acid conjugates employing polyethylene glycol as a soluble support.[9]

Various PEG-bound L-amino acids **4** were obtained by coupling Fmoc-amino acids with monomethoxy-PEG (Aldrich, average Mn ca. 2000). Formation of the amino acid ester was found to be quantitative as revealed by Fmoc analysis. Initial loading of the Fmoc-amino acid was determined by cleavage of a small amount (2 mg) of PEG-bound Fmoc-amino acid by treatment with piperidine (20%) in dichloromethane (3 ml) and subsequent quantitative UV analysis by measuring the relative absorbance at 289 nm. Fmoc cleavage was then effected by treatment with a solution of piperidine in dichloromethane (20%) and the resulting PEG-bound amino acid **4**, isolated after routine precipitation, was allowed to react with acetyl protected glucals derived from various sugars in the presence of a catalytic quantity of $BF_3{\cdot}Et_2O$. All the reactions were conducted at ambient temperature in CH_2Cl_2 for 6 h. Glycosylation of PEG-bound amino acid **4** takes place via the delocalized allyloxocarbenium ion **3** generated by reaction of $BF_3{\cdot}Et_2O$

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* Corresponding author. Tel.: +91 01912572002x292; fax: +91 0191 2548607; e-mail: hmskumar@yahoo.com

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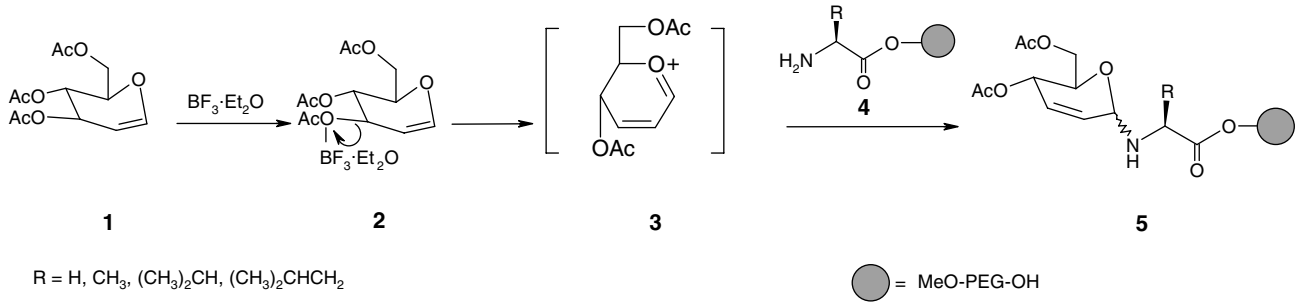
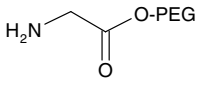
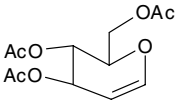
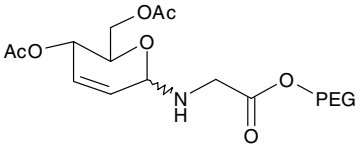
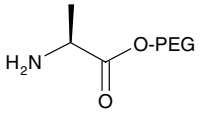
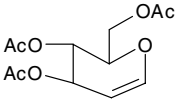
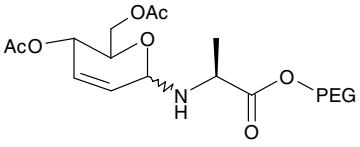
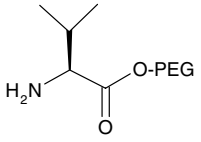
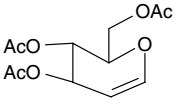
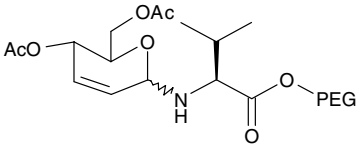
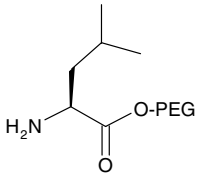
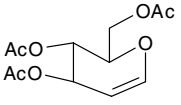
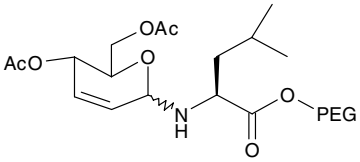
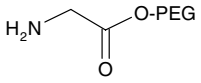
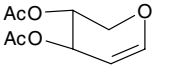
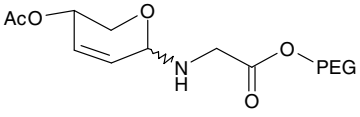
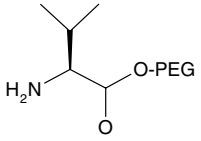
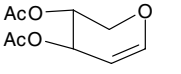
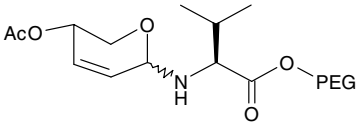


Scheme 1. Ferrier rearrangement for the synthesis of PEG-bound 2,3-unsaturated glycopyranosyl-amino acids.

with tri-*O*-acetyl-D-glucal[10,11] **1** by the nucleophilic attack at the anomeric centre to give 2,3-unsaturated amino acid glycopyranoside **5** (Scheme 1). The formation of 2,3-unsaturated glycosidic amino acid conjugates was confirmed by ^{1}H NMR analysis of the PEG-bound products. The scope of the present method was explored using various amino acids and D-glucals derived from sugars such as tri-*O*-acetyl D-glucal and di-*O*-acetyl D-xylal as shown in Table 1, and it was found to proceed smoothly for all these compounds with quantitative conversions. We also examined other catalysts such as $SnCl_4/CH_2Cl_2$ (0–28 °C), $InCl_3/CH_2Cl_2$ (28 °C) and found that $BF_3{\cdot}Et_2O$ worked better in terms of product formation with PEG-bound amino acids. The product

Table 1. Ferrier rearrangement of unsaturated sugars with PEG-bound amino acids; synthesis of 2,3-unsaturated-*O*-acetyl-amino acid pyranosides

Entry	Amino acid PEG ester	Unsaturated sugar	Product[a]
1			
2			
3			
4			
5			
6			

[a] All PEG-bound compounds were characterized by ^{1}H NMR analysis in $CDCl_3$ and also by cleavage of the PEG-bound product using 3 N NaOH and ^{1}H NMR analysis of the crude product.

was found to be a mixture of α- and β-anomers (α:β ratio 3:2) as estimated by ^{1}H NMR integration of the anomeric signals.

Even though such rearrangements are familiar with sulfonamides and carbamates in solution phase,[12] the same has not been extended to amines and amino acids so far. Furthermore, our solution phase trials of such reactions using amino acid esters gave the rearranged products in moderate yields, for example, reaction of alanine phenacyl ester/$BF_3{\cdot}Et_2O$ gave a 61% yield of the Ferrier product in 6–8 h in dry CH_2Cl_2 under a nitrogen atmosphere.

In conclusion, we have developed an efficient liquid phase methodology for the synthesis of PEG-bound 2,3-unsaturated amino acid glycopyranosides from *O*-acetyl-D-glucals and PEG-bound amino acids through Lewis acid catalyzed Ferrier rearrangement.

Acknowledgements

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9. *Liquid phase synthesis of glycine derived 2,3-unsaturated N-glycopyranoside polymer-supported Fmoc-glycine*: Fmoc-glycine (297.3 mg, 1 mmol), a catalytic amount of HOBt (33.75 mg, 0.25 mmol) and DCC (206 mg, 1 mmol) were added to monomethoxy-PEG (1 g) in dry CH_2Cl_2 (10 ml). The mixture was stirred at rt for 24 h. The precipitated urea was removed by filtration and the filtrate was concentrated to one third of its original volume and then diluted with Et_2O (100 ml). The resulting precipitate was collected through filtration, washed with Et_2O (3×50 ml) and dried in vacuo to afford the polymer-supported Fmoc-amino acid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.46–4.38 (m, PEG), 4.43 (m, 3H, Fmoc-CH– and –CH_2–), 7.54 (m, 4H), 7.65 (m, 2H), 7.77 (2H, d, $J = 7.24$ Hz).
Fmoc-cleavage of PEG-bound glycine: Fmoc cleavage of PEG-glycine was affected by stirring PEG-Fmoc-glycine (500 mg) with 20% piperidine: DCM solution (5 ml) for 2 h. The solvent was evaporated, the residue dissolved in 0.5 ml of DCM and diluted with Et_2O (60 ml). The resulting precipitate was collected, washed with Et_2O and dried to afford the PEG-supported glycine. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.46–4.38 (m, PEG and N–CH_2–COO).
Glycine 2,3-unsaturated N-glycopyranosides—typical procedure: PEG-bound glycine (500 mg) was dissolved in 5 ml of dry DCM under a nitrogen atmosphere. 2,3-Unsaturated-tri-*O*-acetyl-glucal (272 mg, 1 mmol) and BF_3/Et_2O (50 μl) were added to the solution, which was stirred for 6 h under an inert atmosphere. The reaction mixture was concentrated, dissolved in a minimum amount of DCM and then diluted with Et_2O (50 ml). The resulting precipitate was collected through filtration, washed with Et_2O and dried to afford the polymer-supported 2,3-unsaturated-di-*O*-acetyl-glycine glycopyranoside. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.17 (s, 3H), 3.46–4.38 (m, PEG), 5.08 (br s, 1H, H-1 of α), 5.19 (s, 1H, H-1 of β), 5.33 (d, 1H, $J_{4,5} = 9.1$ Hz, H-4), 5.87 (s, 2H, H-2 and H-3 of α), 5.98 (br s, 2H, H-2 and H-3 of β).
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