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Cross-Metathesis of N-Alkenyl Peptoids with O- or C-Allyl Glycosides

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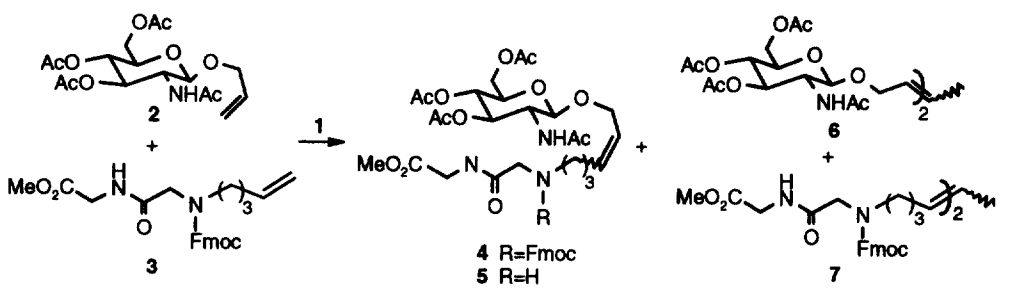
Abstract: Cross-metathesis of several N-alkenyl-containing oligoglycines derivatives (peptoids) with protected O- or C-allyl glycosides of N-acetylglucosamine, galactose, and mannose using Grubbs' ruthenium benzylidene catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ (**1**) has been achieved in 40 to 52% yields.

In view of the potential biological functions of glycopeptidomimetics[1] and of O- or N-linked glycopeptoids in particular,[2] together with the enhanced binding properties of glycoclusters,[3] it was deemed of interest to construct oligomers bearing the features of N-substituted oligoglycines (peptoids).[4] We report herein preliminary results illustrating the successful cross-metathesis reaction between N-alkenyl peptoid derivatives with various O- or C-allyl glycosides using Grubbs' catalyst **1** (Scheme 1).



Scheme 1

Grubbs' catalyst **1** has been rapidly accepted as one of the most useful promotor in several metathesis reactions.[5] In cross-metathesis reaction however, the usefulness of the procedure is greatly limited by steric factors, although recent reports indicated successful applications in carbohydrates when symmetrical disubstituted olefins were used.[6] As shown in a recent study,[7] allylglycine derivatives showed good reactivity with various alkenes, while their analogous vinylglycine derivatives gave no or poor results. Unfortunately, no detailed study has been done to illustrate the limitation of the chain length of N-alkenyl derivatives during intermolecular cross-metathesis. To clarify this point in the construction of oligomeric glycopeptoid libraries, mono N-allyl, butenyl, and pentenyl-containing glycine dimers were prepared.

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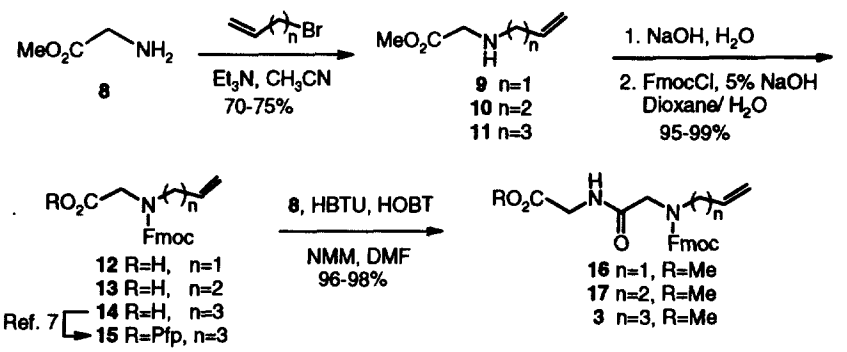
Monosubstituted N-alkenylglycine dimers **3, 15-17** can be readily synthesized from methyl glycinate **8** (Scheme 2). Mono-N-allylation of **8** (CH_2=$CHCH_2Br$, CH_3CN, Et_3N, rt, 10hr) produced N-allyl glycinate **9** in 75% yield. After ester hydrolysis under basic condition (aq. NaOH), the *in situ* generated amine was protected by treatment with 9-fluorenylmethyl chloroformate (FmocCl, NaOH, dioxane:H_2O) to give **12** in 98% overall yield. Following the above procedure, N-butenyl and N-pentenyl glycinate **10-11** were similarly obtained (75%). Base hydrolysis and subsequent Fmoc-protection as above afforded acids **13, 14** in 72 and 75% overall yield (based on **8**), respectively. Treatment of acids **12-14** with methyl glycinate **8** (HBTU, HOBT, NMM, DMF, rt, 4hr) provided dipeptoids **3, 16, 17** in almost quantitative yields. Pentafluorophenyl ester **15** was also obtained from **3** in 80% yield following standard procedure.

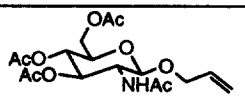
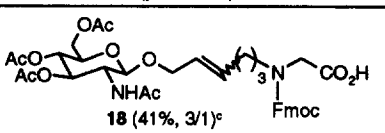
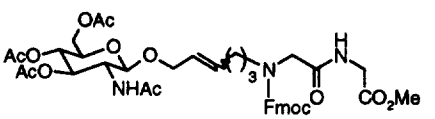
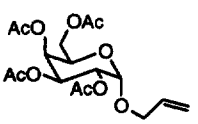
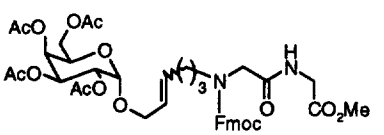
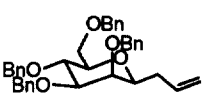
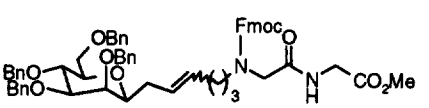
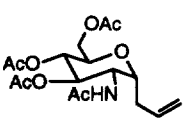
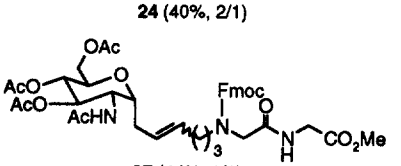
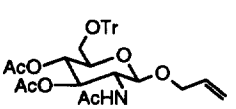
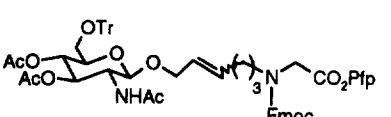


Scheme 2

When peracetylated allyl β-D-GlcNAc glycoside **2**[8] was treated with Grubbs' catalyst **1** in the absence of added alkene (CH_2Cl_2, 25°C), the expected dimer **6** was obtained in 85% yield.[9] However, when N-allylamine derivative **9** was treated with **2** and catalyst **1** (10 mole%), no cross-metathesis took place even under forcing conditions. However, GlcNAc dimer **6** can still be produced in 30% yield. The secondary amine seemed to have poisoned the catalyst and the same held for amine **10**. When N-pentenyl glycinate **11** was subjected to the same reaction conditions, the cross-metathesis proceeded slowly, at the same time, GlcNAc dimer was formed. No cross-metathesis product was detected when **12** and GlcNAc **2** were subjected to the standard metathesis condition. The cross-metathesis of acids **13** and **14** with GlcNAc **2** proceeded smoothly to give the expected cross-metathized products in 30 and 41% yields, respectively (based on the peptoids) together with GlcNAc dimer **6** in 12 and 10% yield. It is noteworthy that even the free carboxylic acids **13** and **14** were still tolerated substrates for the cross-metathesis reaction. Cross-metathesis of **12, 16, 17** with GlcNAc **2** also gave lower yields (0, 18, 30%) when compared to compounds having longer side chains, as seen with N-pentenyl derivatives **3, 11, 14, 15**. Peptoids **3, 15, 16** were subjected to cross-metathesis reaction with a wide range of O- and C-allyl glycosides **2, 20, 23, 26,** and **29** bearing different anomeric compositions and protecting groups (see Table 1).

Stoichiomeric amounts of both alkene derivatives were used. The desired cross-products **4, 18, 21, 24, 27,** and **30** were obtained in yields ranging from 40 to 52% and as unseparated mixtures of *E/Z* stereoisomers (1:1 to 3:1) with the *E* isomers predominating. The ratios of *E* and *Z* isomers were determined from the ^{1}H NMR spectrum of the crude mixtures according to established γ-effect.[10] Side-products resulting from self-metathesis of the carbohydrate and peptoid derivatives were obtained in 10-20% yields. Table 1 shows that there was no major reactivity differences between α- and β-allyl glycosides when treated with the same peptoid. When the metathesis product **4**, was treated with 20% piperidine in DMF, the deprotected compound **5** was obtained in 98% yield.[11]

Table 1. Metathesis of peptoids and sugars.[a]

Peptoids	Sugar	Cross-metathesis (yield,[b] E/Z)	Sugar dimer (yield,[b] E/Z)	Peptoid dimer (yield,[b] E/Z)
14	 **2**	 **18** (41%, 3/1)[c]	**6** (10%, 2/1)	**19** (10%, 1/1)
3	**2**	 **4** (49%, 1/1)	**6** (11%, 2/1)	**7** (27%, 5/4)
3	 **20**	 **21** (52%, 1/1)	**22** (20%, 4/3)	**7** (18%, 1/1)
3	 **23**	 **24** (40%, 2/1)	**25** (15%, 3/1)	**7** (22%, 1/1)
3	 **26**	 **27** (44%, 1/1)	**28** (14%, 2/1)	**7** (22%, 1/1)
15	 **29**	 **30** (46%, 1/1)	**31** (12%, 2/1)	**32** (16%, 1/1)

[a] Reactions were run according to a general procedure.[11]
[b] Isolated yields.
[c] When 1.2 eq of **2** was used, the cross-metathesis product **18** was obtained in 45% yield.

In conclusion, the cross-metathesis of several O- or C-allyl glycosides and peptoids in the presence of Grubbs' catalyst has been studied. Attachment of peptoids to solid phase and cross-metathesis with several glycosides produced cross-metathesis products in more than 70% yields since excess reagents can be used. The strategy can thus be used to generate combinatorial libraries by utilizing different peptoids, glycosides and repeating units. This work is currently under further investigation.

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References and notes

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10. Breitmaier, E. and Voelter, W. *Carbon -13 NMR Spectroscopy. High Resolutions Methods and Applications in Organic Chemistry and Biochemistry,* VCH, New York, **1987**, pp.192-195.
11. All new compounds gave satisfactory spectroscopic data. General procedure: to a sugar (0.1 mmole) and peptoid (0.1 mmole) solution in CH_2Cl_2 (1.0 mL) under nitrogen was added Grubbs' catalyst (8.23 mg, 0.01 mmole). After stirring for 24h at room temp., the resulting solution was concentrated in *vacuum*. The residual oil was taken up in ether and stirred overnight under air to decompose the catalyst. Removal of the solvent in *vacuum* followed by silica gel chromatography yielded a mixture of isomers (*E/Z* and amide conformers) as a colorless gum. Compound **4** was deprotected (20% piperidine, CH_2Cl_2) to produce **5** (only *E* isomer): ^{1}HNMR (500MHz, $CDCl_3$) δ 5.85 (d, J=8.6Hz, 1H), 5.65 (m, 1H), 5.52 (m, 1H), 5.30 (dd, J=10.5, 9.3Hz, 1H), 5.02 (dd, J=9.8, 9.5Hz, 1H), 4.71 (d, J=9.3Hz, 1H), 4.24 (m, 2H), 4.10 (dd, J=12.2, 2.5Hz, 1H), 4.06 (dd, J=5.6, 1.8Hz, 2H), 4.01 (dd, J=12.2, 6.8Hz, 1H), 3.73 (s, 3H), 3.67 (m, 1H), 3.34 (s, 2H), 2.54 (m, 2H), 2.06 (s, 3H), 2.10 (m, 2H), 2.00 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H), 1.59 (m, 2H). ^{13}C NMR: δ 171.8, 170.8, 170.3, 169.4, 134.5, 125.9, 99.2, 72.3, 71.6, 69.5, 68.8, 62.1, 54.8, 52.3, 52.0, 49.3, 40.7, 29.7, 28.8, 20.7. HRMS calc for $C_{25}H_{39}N_3O_{12}$ 574.2612, found 574.2624.