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Poly(ethylene glycol) Supported Synthesis of Aminoacid Derivatives via Ring Closing Metathesis or Microwave-assisted Alkylation

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Abstract: Ring closing metathesis has been performed for the first time on a soluble poly(ethylene glycol) supported substrate in the presence of Grubbs' catalyst and provided in good yields 6-, 7- and 8-membered ring aminoacid derivatives. The presence of the polymer required the use of a higher amount of ruthenium complex but the addition of a cofactor such as 1-octene improved the turnover of the catalyst. On the other hand, a Schiff base protected glycine supported on a poly(ethylene glycol) reacted readily with various electrophiles in the presence of an inorganic base under microwave activation.

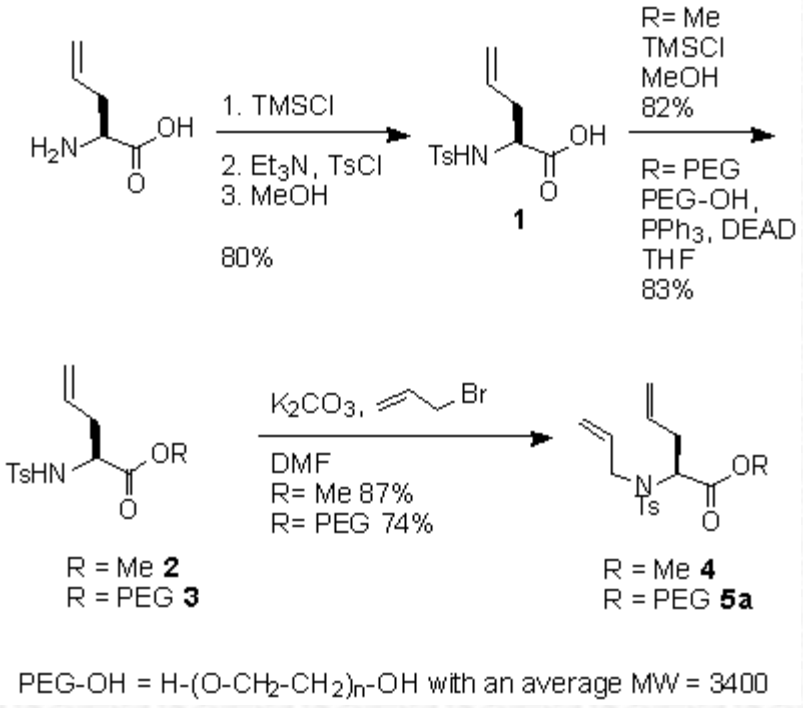
1. Synthesis of cyclic aminoacid derivatives via Ring Closing Metathesis

Liquid phase organic synthesis where soluble polymers such as poly(ethylene glycol) (PEG) are used as polymeric support is a practical alternative to solid phase organic synthesis (SPOS).[1] Recently we have developed several PEG-supported syntheses of aminoacid derivatives[2] and we have studied the effect which can be induced by the polymer. Because of its polyoxygenated structure, the polymer exerts an influence on the reactivity of the supported reacting center as well as on the reagents or catalysts used during the course of the synthesis. We have shown that a synthesis of arylglycine using organozinc reagents could not be adapted on PEG because of the detrimental effect of the polymer.[2e] On the contrary in the case of a Heck reaction used in the synthesis of glutamic acid analogs, PEG has an accelerating effect on the course of the reaction.[2c]

Ring closing metathesis (RCM) has emerged as a powerful tool in organic synthesis for generating cyclic structures via C-C bond formation.[3] Recently this reaction has been adapted to SPOS[4] but to our knowledge no reaction of RCM on soluble PEG has been published. In the following report, we present the results obtained in investigating the compatibility of RCM reaction conditions with the presence of PEG and we describe the synthesis of various aminoacid derivatives using this method.

Since our interest lies in the synthesis of aminoacids and peptidomimetics, we chose to adapt first the synthesis of a cyclic aminoacid[5] and we compared the results obtained with the molecule supported on PEG with the

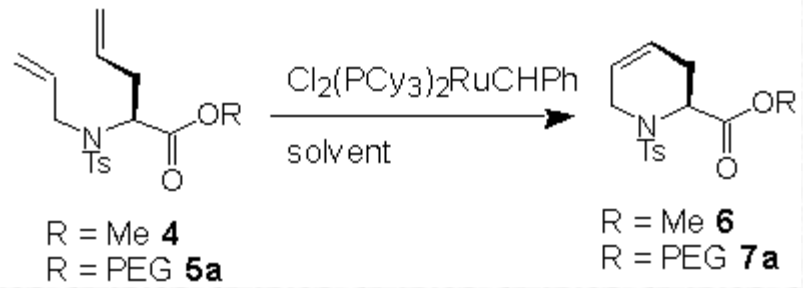
same reaction carried out in solution. Linear substrates **4** and **5a** were synthesized as described in scheme 1.



Scheme 1

Since it was preferable to obtain at each step of the synthesis on the soluble support complete conversion of the starting material to the expected product, we decided to use a tosyl group as a nitrogen protecting group which also makes the amine proton more acidic for the alkylation reaction. Tosylation of commercially available (L)-allylglycine was adapted from a known procedure.[6] Esterification of **1** with MeOH in the presence of TMSCl yielded **2** which was smoothly *N*-alkylated with allyl bromide in the presence of potassium carbonate to give **4**. Bifunctional poly(ethylene glycol) with an average mass of 3400 was used as the soluble support because it presents the right compromise between loading and good precipitation properties.[2b] Since the Ts group made allylglycine sensitive to racemization, we preferred to avoid classical coupling conditions and we chose a Mitsunobu reaction for anchoring the Ts allylglycine **1** on both of the hydroxyl groups of the PEG to give **3**.[7] Alkylation with allyl bromide in the presence of potassium carbonate yielded the PEG supported *N*-allyl allylglycine **5a**.

Linear substrates **4** and **5a** were submitted to classical RCM reaction conditions using Grubbs' catalyst in various amounts (scheme 2).



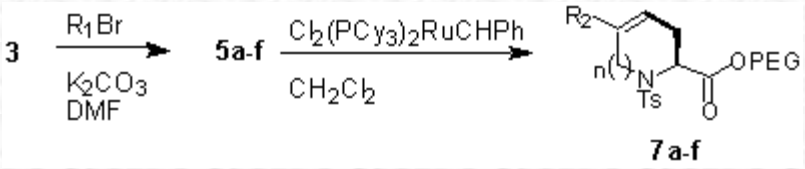
Scheme 2

The best conditions we found in order to cyclize **5a** were to use 40 mol% of catalyst at room temperature and then the reaction was complete within 8h. The cyclization was also carried out under microwave activation[8]. 50 mol% of the ruthenium catalyst was needed for cyclizing **5a** in the absence of solvent but in this case the

reaction time was dramatically reduced (from 8 h to 10 min). When the reaction was carried out with 2 equiv of 1-octene, it was possible to cut by half the amount of catalyst used (20 mol%) but so far we were not able to drop further this amount even when employing a larger quantity of 1-octene.

Table 1 presents various examples of ruthenium-catalyzed cyclizations which led to the synthesis of amino acid derivatives. PEG supported (L)-allylglycine **3** was readily alkylated with different bromides to yield linear substrates **5a-f** which were cyclized to **7a-f**.

Table 1. Examples of RCM for the synthesis of cyclic amino acid derivatives.



entry	R_1-	**5**	cat. mol%	n	R_2	Yield of **7** (%)
1	Allyl-	**a**	20[a]	1	H	92
2	$PhCH=CHCH_2$-	**b**	40	1	H	86
3	$H_2C=CH(CH_3)$-	**c**	40	1	CH_3	95
4	$H_2C=CH(CH_2)_2$-	**d**	40	2	H	90
5	$H_2C=CH(CH_2)_3$-	**e**	40	3	H	82
6	$HC\equiv C-CH_2$—	**f**	40[a]	1	$CH=CH_2$	80

[a]2 equiv of 1-octene were used

In order to release the Ts amino acid from the polymer, a racemization free acidic hydrolysis was performed (in refluxing 6N HCl for 4 h) and the free acids were obtained in good yields.

We have presented here the first examples of RCM on a soluble PEG supported substrate. Although a relatively high amount of catalyst was needed, this method allows for the efficient synthesis of optically active cyclic amino acid derivatives with various ring sizes. Further investigation to improve the catalytic efficiency of this reaction is under study in our laboratory.

Representative procedure: Poly(ethylene glycol)-3400 Di((*L*)-*N*-tosyl-4,5-didehydropipecolate) (7a): The ruthenium catalyst (0.002 g, 0.003 mmol) was added to a solution of **5a** (0.050 g, 0.013 mmol) and 1-octene (0.003 g, 0.026 mmol) in 5 mL of CH_2Cl_2, the mixture was stirred at room temperature for 8 h, then precipitated in Et_2O twice. The product was filtered and dried in vacuo to yield 0.047 g (92%) of the title compound : IR (KBr) 2359 (s), 1484 (w), 1349 (m), 1113 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) d 2.45 (s, 6 H), 2.55 (sl, 4 H), 3.50-3.70 (large s, ~ 310 H), 4.90 (t, *J* = 4.0 Hz, 2 H), 5.70 (s, 4 H), 7.30 (d, *J* = 8.5 Hz, 4 H), 7.70 (d, *J* = 8.5 Hz, 4 H); ^{13}C NMR ($CDCl_3$, Me_4Si) d 21.93, 28.21, 42.52, 52.89, 64.43, 68.96, 70.92, 122.50, 123.86, 127.65, 129.85, 136.66, 143.64, 170.67

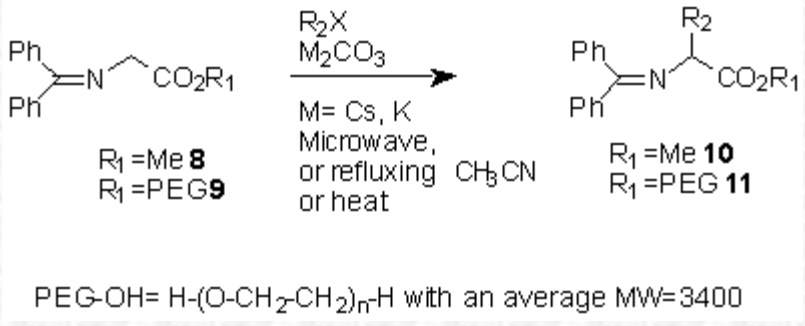
2. Synthesis of aminoacid derivatives via Microwave-assisted Alkylation

Microwave-assisted organic synthesis has become an increasingly used technique for the generation of new molecules.[9] It leads usually to shorter reaction times and increased yields and purity. Many solvent-free reactions using microwaves have been developed since it reduces the risks of hazards by pressure build up in the reaction vessel and the scale-up is made easier. One particularly attractive field is the coupling of microwave activation with the solvent-free phase-transfer catalysis (PTC) [10] where a reactant can also act as the organic phase. We report herein a PTC reaction in which a polymer support serves also as the organic phase.

In an ongoing project dealing with the supported synthesis of a-aminoacid derivatives[2] we developed a phase-transfer catalyzed alkylation of a Schiff base glycine supported on a soluble poly(ethylene glycol) polymer (PEG) (scheme 3). [2a,b] Initially the reaction was carried out in acetonitrile using an insoluble inorganic base such as K_2CO_3 or Cs_2CO_3 in the presence of various electrophiles. We have shown that in such a reaction the soluble polymer could act as a phase-transfer catalyst. [2a-c]

Since PEG of low molecular weight (400 to 800) have received attention as solvent in a wide variety of reactions,[11] we have decided to investigate the possibility of using a PEG simultaneously as polymeric support and solvent. The PEG which we used has an average molecular weight of 3400 and was functionalized at both ends.[2b] A PEG supported molecule such as **9** is solid at room temperature with a melting point of 45-47°C. Therefore we thought that a reaction could be carried out in the absence of an extra solvent as long as the conditions would melt the polymeric molecule. Microwave heating was then considered to provide conditions for a solid-liquid phase-transfer catalysis to occur. [12,13]

The reaction test which was chosen was the alkylation[14] by benzyl bromide in the presence of different inorganic bases (K_2CO_3 or Cs_2CO_3) of two different substrates, one in the absence of PEG (**8**) and one supported on PEG (**9**). For the sake of comparison, reactions were performed under microwave activation[15] or in refluxing acetonitrile or with conventional heating without extra solvent. The alkylation results are presented in Table 2.



Scheme 3

Table 2. Reaction time for complete alkylation of **8** and **9** with benzyl bromide[a]

entry	Starting material	Reaction conditions	Reaction time (min)	
			Cs_2CO_3	K_2CO_3
1	**8**	Microwave	60	90
2	**9**	Microwave	35	40
3	**8**+	Microwave	40	45

	PEG-OMe			
4	**8**+ 5mol% PEG-OMe	Microwave	50	-b
5	**9**	refluxing acetonitrile	60	300
6	**9**	heating at 85°C	45	120

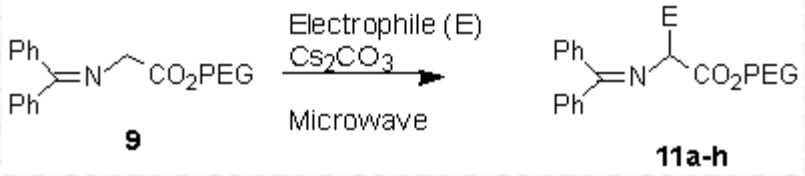
[a] Experimental conditions : 1 equiv of activated methylene, 1.5 equiv of $PhCH_2Br$. [b]Not performed.

In all cases the reaction went to completion in a reasonable amount of time with both of the inorganic bases with reaction time being shorter with Cs_2CO_3 than with K_2CO_3. The reaction performed on the PEG supported Schiff base **9** was faster than the one performed on **8** in the absence of PEG (entry 2 vs entry 1). This effect of PEG was confirmed by running the reaction of **8** in the presence of PEG-OMe (entry 3). Also in this case the reactions were accelerated. In these reactions the acceleration of the reaction kinetics could be interpreted by the fact that after the PEG has melted at the temperature reached in the microwave oven, it provided a solvent environment which could conduct the heat and diffuse the chemicals. Moreover this is a solvent with special properties since it can chelate cations efficiently and accelerate the alkylation as we have shown before.[2a,b] Entry 2 illustrates clearly the fact that a poly(ethylene glycol) could be used simultaneously as solvent and polymeric support.

We compared two different mode of activation of **9**, under microwave in the absence of extra solvent (entry 1) and in refluxing acetonitrile (entry 5). For both of the bases the reaction times were shorter under microwave activation, especially in the case of K_2CO_3.

In all cases, reactions with K_2CO_3 were slower than with Cs_2CO_3 and also more sensitive to the reaction conditions. Whereas the reaction times with Cs_2CO_3 were in the same order of magnitude, large differences were met with K_2CO_3. The effects of PEG are more sensitive with the potassium cation most probably because of a more important chelation effect due to the size of the cation.

Schiff base **9** was then reacted with various electrophiles (scheme 4) and the results are presented in Table 3.



Scheme 4

Table 3. Alkylation of **9** with various electrophiles.

entry	**11**	E	Reaction time	Yield (%)

			(min)	
1	a	$PhCH_2Br$	35	90
2	b	$CH_2=CHCH_2Br$	40	94
3	c	CH_3CO_2 $(CH_3)CHCH_2Br$	40	75
4	d	$(CH_3)_2CHCH_2I$	30	89
5	e	$PhCH=CHCH_2Br$	45	98
6	f	n-PentBr	60	93
7	g	$H_2C=CHCO_2Me$	45	97
8	h	$H_2C=C(CH_3)CO_2Me$	60	83

These examples showed that diverse electrophiles could be used in this reaction, including acrylic acid derivatives.[16] After alkylation, the aminoester was released from the polymer by transesterification with MeOH in the presence of Et_3N.[2b,17] This confirmed the possibility of performing microwave-assisted parallel synthesis of aminoacid derivatives supported on poly(ethylene glycol) without extra solvent[18] and it could be extended to other small organic molecules. Microwave assisted solid-phase synthesis of organic molecules has also been reported [19] but so far it seemed that an extra solvent was necessary and that sometimes degradation of the polymer support was observed. [19a]

In summary we have shown that poly(ethylene glycol) with a molecular weight of 3400 could serve as a solvent in microwave assisted reactions. These reactions can be performed when the PEG acts also as the support. No specific microwave effects could be found but this technique remains more practical than conventional heating and could be more widely applied to combinatorial chemistry.

Representative procedure: Synthesis of **11e** : Cinnamyl bromide (11.8 mg, 0.06 mmol) was added to poly(ethylene glycol) 3400 N-(diphenylmethylene) glycinate (80 mg, 0.02 mmol) and Cs_2CO_3 (39 mg, 0.12 mmol). The mixture was heated under microwave for 45 minutes. After cooling, the product was dissolved in CH_2Cl_2, then filtered. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then, precipitated in Et_2O. The product was filtered and dried in vacuo to yield 80 mg (98 %) of the title compound : IR (KBr) 2865 (m), 1736 (s), 1655 (s), 1459 (s), 1100 (m), 954 (m) cm^{-1} ; ^1H NMR ($CDCl_3$, Me_4Si) d 2.70-2.90 (m, 2 H), 3.50-3.80 (s large, 310 H), 4.05 - 4.15 (m, 1 H), 4.20 - 4.30 (m, 2 H), 5.90-6.15 (m, 1 H), 6.30-6.45 (d, *J*= 15.5 Hz, 1 H), 7.10-7.40 (m, 13 H), 7.55-7.70 (m, 2 H) ; ^{13}C NMR ($CDCl_3$, Me_4Si) d 37.48, 64.44, 65.78, 69.36, 126.40, 127.49, 128.27, 128.40, 128.83, 128.86, 129.03, 129.18, 130.73, 133.08, 136.72, 137.68, 139.85, 171.17, 171.99

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