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Poly(ethylene glycol) as solvent and polymer support in the microwave assisted parallel synthesis of aminoacid derivatives

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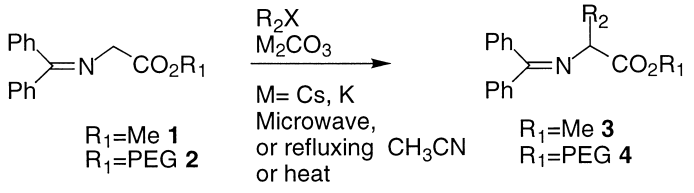
Abstract

A Schiff base protected glycine supported on a soluble polymer such as poly(ethylene glycol) reacted readily with various electrophiles in the presence of an inorganic base under microwave activation. It was shown in this study that the polymer support also serves as solvent in these reactions. Various α-aminoacids derivatives could be synthesized using this method.

Microwave-assisted organic synthesis has become an increasingly used technique for the generation of new molecules.[1] It usually leads 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),[2] 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 α-aminoacids derivatives,[3,4] we developed a phase-transfer catalyzed alkylation of a Schiff base glycine supported on a soluble poly(ethylene glycol) polymer (PEG) (Scheme 1).[3] Initially the reaction was carried out in



PEG-OH= H-(O-CH_2-CH_2)$_n$-H with an average MW=3400

Scheme 1.

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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.[3,4a]

Since PEG of low molecular weight (400 to 800) have received attention as solvent in a wide variety of reactions,[5,6] 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.[3b] A PEG supported molecule such as **2** 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.[7,8]

The reaction test which was chosen was the alkylation[9] 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 (**1**) and one supported on PEG (**2**). For the sake of comparison, reactions were performed under microwave activation[10] or in refluxing acetonitrile or with conventional heating without extra solvent. The alkylation results are presented in Table 1.

Table 1
Reaction time for complete alkylation of **1** and **2** with benzyl bromide[a]

entry	Starting material	Reaction conditions	Reaction time (min)	
			Cs_2CO_3	K_2CO_3
1	**1**	Microwave	60	90
2	**2**	Microwave	35	40
3	**1**+ PEG-OMe	Microwave	40	45
4	**1**+ 5mol% PEG-OMe	Microwave	50	-[b]
5	**2**	refluxing acetonitrile	60	300
6	**2**	heating at 85° C	45	120

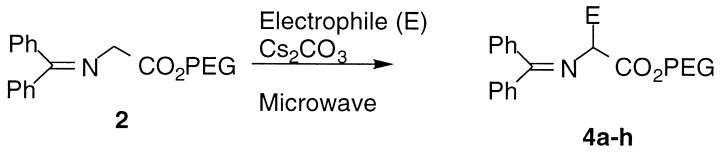
[a]Experimental conditions : 1 equiv of activated methylene, 1.5 equiv of $PhCH_2Br$. [b]Not performed.

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 **2** was faster than the one performed on **1** in the absence of PEG (entry 2 vs entry 1). This effect of PEG was confirmed by running the reaction of **1** in the presence of PEG-OMe (entry 3). In this case the reactions were also accelerated. A submolar amount of PEG (5 mol%) was also used but appeared to be less efficient (entry 4). 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.[3] Entry 2 clearly illustrates the fact that a poly(ethylene glycol) could be used simultaneously as solvent and polymeric suppport.

We then compared two different mode of activation of **2**, 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. One might question whether this effect was intrinsically produced by the microwave irradiation[2] or whether it was due only to the fact that a temperature higher than 85°C was reached in the reaction vessel. Another explanation could be that neat PEG was more efficient as a solvent and phase-transfer catalyst than a mixture acetonitrile/PEG. We therefore chose to run the reaction under classical thermal conditions without extra-solvent. The choice of the reaction temperature was then a critical parameter for comparison. At this point we were reaching the limits of the microwave oven we were using since it was difficult to measure the temperature reached at the end of the reaction on the quantities of substrate we were using. Also, being a multimode oven, this temperature might not be stable during the irradiation time. We finally chose to carry out the reaction at 85°C (temperature of the oil bath; entry 6), which would also provide for some comparison with the refluxing acetonitrile conditions. In this case the reaction time was longer than the one obtained under microwave (entry 2) but shorter than the one in refluxing acetonitrile (entry 5). Microwave irradiation did not dramatically shorten the reaction times which seems to confirm that specific effects other than heating were not involved in this reaction. These experiments also confirmed that neat PEG was a better solvent than acetonitrile and could strongly enhance the reactivity of the inorganic base by chelation of the countercation. Abribat et al.[6d] have also noticed the increased catalytic efficiency of PEG in the absence of a co-solvent in a Williamson ether synthesis. Berdagué et al.[6a] have defended the idea that activation generated by a PEG could be modulated by adding a cosolvent: they described the bis *O*-alkylation of a dihydroxybenzene carried out when PEG was used as the only solvent whereas selectivity could be directed towards the mono *O*-alkylation when a co-solvent was added.

Finally, 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 **2** was then reacted with various electrophiles (Scheme 2) and the results are presented in Table 2.



2 **4a-h**

Scheme 2.

These examples showed that diverse electrophiles could be used in this reaction, including acrylic acid derivatives.[11] After alkylation, the aminoester was released from the polymer by trans-esterification with MeOH in the presence of Et_3N.[3b,12] This confirmed the possibility of performing microwave-assisted parallel synthesis of aminoacid derivatives supported on poly(ethylene glycol) without extra solvent,[13] and it could be extended to other small organic molecules. Microwave assisted solid-phase synthesis of organic molecules has also been reported,[14] but so far it seemed

Table 2
Alkylation of **2** with various electrophiles

entry	4	E	Reaction time (min)	Yield (%)
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

that an extra solvent was necessary and that sometimes degradation of the polymer support was observed.[14a]

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 also acts 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.

Acknowledgements

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