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Polyethylene Glycol (PEG) as Polymeric Support and Phase-transfer Catalyst in the Soluble Polymer Liquid Phase Synthesis of α-Amino Esters

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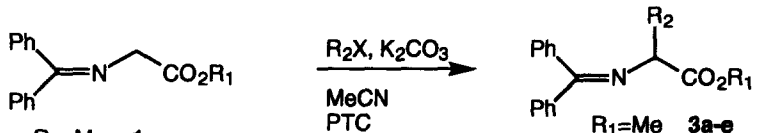
Abstract: α-substituted α-amino esters were synthesized in liquid-phase by polyethylene glycol (PEG) promoted alkylation of a polyethylene glycol-supported Schiff base activated glycine ester.

The liquid phase method, known for more than 25 years in peptide synthesis,[1] has been recently applied to the synthesis of small organic molecules and to combinatorial chemistry.[2] Using soluble polymers support such as polyethylene glycol (PEG), this method combines the strategical features of solution and solid phase methods. The synthesis is carried out in homogeneous solution while purification is performed by precipitation of the polymer. Furthermore, molecules anchored to soluble polymers can be readily characterized by NMR spectroscopy.

In an ongoing research project toward the development of efficient and facile methods for the synthesis of α-amino acids,[3] it seemed attractive to use this methodology for synthesizing α-substituted α-amino acids. We decided to adapt a simple and efficient method developed initially for the solution synthesis of α–amino acids : the phase-transfer catalyzed alkylation of Schiff base activated glycine ester **1** using a mild non-nucleophilic base, K_2CO_3 (Scheme 1, R_1=Me).[4] The reaction was catalyzed by a quaternary ammonium salt especially when the reactivity of the electrophile was poor (R_2= *n*-Bu). Recently PEG have received increasing attention as phase-transfer catalyst and have shown their efficiency for the formation of a carbon-carbon bond by substitution or elimination reactions.[5] In this paper we report that PEG present as a polymeric support can also act as a catalyst during the course of the reaction. Consequently the use of a quaternary ammonium salt is not necessary. The alkylation which was studied is described in Scheme 1 (R_1=PEG) starting from the Schiff base activated glycine PEG ester **2** as the starting material and various electrophiles R_2X.

Scheme 1



PTC=$(n\text{-}C_4H_9)_4N^+B^{r-}$ or MeO-PEG

PEG=H-(O-CH_2-CH_2)n-OH

The preparation of the starting material **2** is described in Scheme 2. Polyethylene glycol with an average molecular weight of 2000 and two free hydroxyl groups was used instead of the usual HO-PEG-OMe

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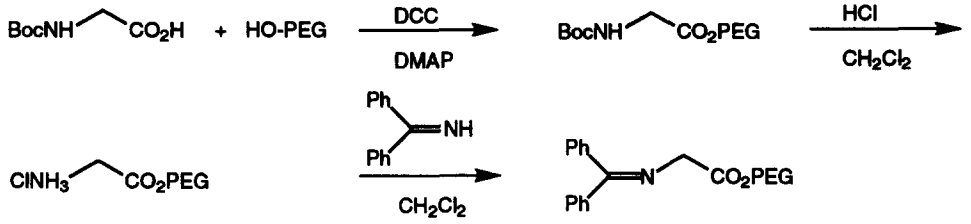
with an average molecular weight of 5000. This resulted in increasing the loading of the polymer by a factor of 5. In some cases precipitation in ether for purification was more cumbersome producing slightly lower yields of the expected products.

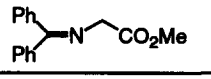
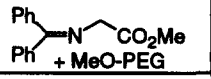
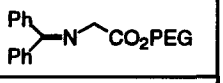
Scheme 2



Protected Boc glycine was anchored to the polymer using DCC as coupling agent in the presence of DMAP.[6] Deprotection using HCl and transimination with benzophenone imine afforded starting material.[7] Purification was performed by precipitation in Et_2O and the products were characterized by IR spectroscopy and ^1H and ^{13}C NMR.

The test reaction which was examined to investigate the effect of PEG on the rate of substitution was the alkylation described in Scheme 1 performed in refluxing acetonitrile using K_2CO_3 as a base, 1.5 equivalents of *n*-BuBr as the electrophile and in the absence of a quaternary ammonium salt. The rate of alkylation of PEG supported Schiff base **2** was compared to the rate of alkylation of Schiff base **1** by itself and to the rate of alkylation of Schiff base **1** in the presence in solution of a PEG. In these reactions only the starting material and the expected product were observed by ^1H NMR and the ratio of starting material/expected product is reported in Table 1.

Table 1. Effect of PEG on the kinetics of the alkylation

		Entry 1	Entry 2	Entry 3
				
ratio starting material/ expected product		**1/3a**	**1/3a**	**2/4a**
Reaction time	14h	92/8	57/43	77/23
	24h	-	20/80	41/59
	36h	77/23	0/100	0/100

MeO-PEG= polyethylene glycol dimethyl ether with an average molecular weight of 2000

In the absence of PEG (entry 1) after 36h only 23% of conversion is observed while PEG supported Schiff base **2** (entry 3) was completely converted into the alkylated product, clearly indicating an accelerating effect of PEG on the reaction rate. This result was confirmed by examining the reaction rate of Schiff base **1** in the presence of PEG which showed a similar effect on the reaction rate. In this case the reaction rate seemed to be slightly higher than for the PEG supported Schiff base **2**. These effects can be explained by a possible chelation of the potassium ion by the oxygen atoms of the PEG molecules. Indeed it has been shown that PEG have the ability to form chelates like a crown ether therefore resulting in the solvation of the potassium cation and in an acceleration of the reaction.[8] When the Schiff base is anchored on the PEG (entry 3) the rate is

slower than with "free" Schiff base 1 and PEG (entry 2) : this seems to point out that the accessiblity of the Schiff base anchored on the polymeric support is somewhat more limited probably because of an aggregation phenomenon of the polymer.

The same procedure was used to synthesize additionnal α-amino esters (Table 2). Because of the higher electrophilicity of the halides which were used, shorter reaction times were necessary (14 h). In all cases, only the expected product was obtained with moderate to good yields.[9] The α-amino esters synthesized by this method could be either used for further reaction on solid-support such as in peptide synthesis after N-deprotection with TFA[1a,b] or released from the polymer via transesterification with methanol (scheme 2).[1c,10]

Scheme 2

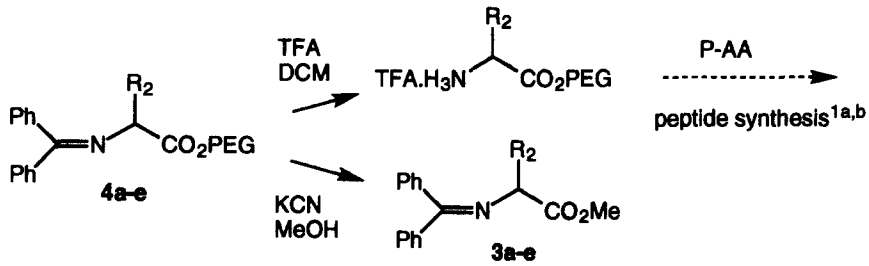
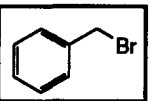


Table 2. Synthesis of α–substituted α–aminoesters

R_2X	*n*-BuBr				
Alkylated PEG Ester	**4a**	**4b**	**4c**	**4d**	**4e**
Yield (%) of 4	68	78	71	65	74
Yield (%) of 3 (from 4)	67	69	73	54	75

In summary, we have shown that a poylethylene glycol polymer could act both as support and phase-transfer catalyst in liquid-phase synthesis. This provides us with an efficient and practical method for the synthesis of α–substituted α-amino esters.

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References and Notes

1. a. Mutter, M.; Bayer, E. In *The Peptides; Analysis, Synthesis and Biology*; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1980 ; Vol. II, p 286-332. b. Pillai, V. N. R.; Mutter, M. *Acc. Chem. Res.* **1981**, *14*, 122-130. c. Zhu, J.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 5831-5837.
2. a. Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489-509. b. Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6419-6423.
3. Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **1997**, *38*, 3385-3386.
4. a. O'Donnell, M. J.; Esikova, I. A.; Mi. A; Shullenberger, D. F.; Wu, S. *Amino Acid and Peptide Synthesis Using Phase Transfer Catalysis* In *Phase Transfer Catalysis, Mechanisms and Syntheses;* Halpern, M. E., Ed.; ACS Symposium Series: Washington DC, 1996, p 124-135. b. O'Donnell, M. J.;

Wojciechowski, K.; Ghosez, L.; Navarro, M.; Sainte, F.; Antoine, J.-P. *Synthesis* **1984**, 313-315. c. Ezquerra, J.; Pedregal, C.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *Tetrahedron Lett.* **1993**, *34*, 8535-8538. An alkylation in the solid phase of a Schiff base activated glycine ester using organic bases was described by O'Donnell : O'Donnell, M. J.; Zhou, C.; Scott, W.L. *J. Am. Chem. Soc.* **1996**, *118*, 6070-6071.

5. a. Brändström, A. *Acta Chem. Scand.* **1956**, *10*, 1197-1198. b. Lehmkuhl, H.; Rabet, F.; Hauschild, K. *Synthesis* **1977**, 184-186. c. Fornasier, R.; Montanari, F.; Podda, G.; Tundo, P. *Tetrahedron Lett.* **1976**, 1381-1384. d. Santaniello, E.; Manzocchi, A.; Sozzani, P. *Tetrahedron Lett.* **1979**, 4581-4582. e. Tarchini, C.; Anh, T. D.; Jan, G.; Schlosser, M. *Helv. Chim. Acta* **1979**, *62*, 635-640. f. Yanagida, S.; Takahashi, K.; Okahara, M. *J. Org. Chem.* **1979**, *44*, 1099-1103. g. Zupančič, B.; Kokalj, M. *Synthesis* **1981**, 913-915. h. Gokel, G. W.; Goli, D. M.; Schultz, R. A. *J. Org. Chem.* **1983**, *48*, 2837-2842. i. Kimura, Y.; Regen, S. L. *J. Org.Chem.* **1982**, *47*, 2493-2494, *ibid.* **1983**, *48*, 195-198. j. Kimura, Y.; Kirszensztejn, P.; Regen, S. L. *J. Org. Chem.* **1983**, *48*, 385-386. k. Suzuki, N.; Kaneko, Y.; Nomoto, T.; Izawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1523-1524. l. Harris, J. M.; Paley, M. S.; Sedaghat-Herati, M. R.; McManus, S. P. *J. Org. Chem.* **1985**, *50*, 5230-5233.
6. a. Zalipsky, S.; Gilon, C.; Zilkha, A. *J. Macromol. Sci. Chem.* **1984**, *A21(6&7)*, 839-845. b. Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 10150-10155.
7. The corresponding reaction in solution phase is described in the following reference : O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663-2665.
8. a. Chan, L. L.; Wong, K. H.; Smid, J. *J. Am. Chem. Soc.* **1970**, *92*, 1955-1963. b. Yanagida, S.; Noji, Y.; Okahara, M. *Tetrahedron Lett.* **1977**, 2893-2894. c. Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532-1536. d. Balasubramanian, D.; Sukumar, P.; Chandani, B. *Tetrahedron Lett.* **1979**, 3543-3544. e. Bartsch, R. A.; Yang, I. W. *Tetrahedron Lett.* **1979**, 2503-2504. f. Stott, P. E.; Bradshaw, J. S.; Parish, W. W. *J. Am. Chem. Soc.* **1980**, *102*, 4810-4815. g. Slaoui, S.; Le Goaller, R.; Pierre, J. L.; Luche, J. L. *Tetrahedron Lett.* **1982**, *23*, 1681-1684. h. Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 555-563. i. Neumann, R.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 616-617. j. Osowska-Pacewicka, K.; Alper, H. *J. Org. Chem.* **1988**, 53, 808-810. k. Berdagué, P.; Perez, F.; Courtieu, J.; Bayle, J. P. *Bull. Soc. Chim. Fr.* **1993**, *130*, 475-480. l. Abribat, B.; Le Bigot, Y. *Tetrahedron* **1997**, *53*, 2119-2124. m. Kavitake, B. P.; Salunkhe, M. M.; Wadgaonkar, P.P. *Synth. Commun.* **1997**, *27*, 1703-1710.
9. A representative procedure for the synthesis of **4c** is as follow: PEG supported Schiff base **1** (1.22 g, 0.5 mmol), methyl 2-bromomethylacrylate (0.27 g, 1.5 mmol) and K_2CO_3 (0.32 g, 3 mmol) were refluxed in 20 mL of MeCN for 14 h. After cooling, the reaction mixture was filtered, concentrated, dissolved in CH_2Cl_2 and precipitated in Et_2O. The precipitate was filtered and dried in vacuo over P_2O_5 yielding 0.93 g (71%) of **4c** : IR 1726 (s), 1650 (m), 1632 (m), 1249 (m), 1104 (s) cm-1; ^1H NMR ($CDCl_3$, Me_4Si) δ 2.84 (dd, J_1=13.5 Hz, J_2=9 Hz, 4H), 3.07 (dd, J_1=13.5 Hz, J_3=4 Hz, 4H), 3.25-4.10 (m with a peak at 3.53, *ca* 245 H), 4.20-4.50 (m, 6H), 5.64 (s, 2H), 6.22 (s, 2H), 7.10-7.70 (m, 20H); ^{13}C NMR δ 36.31, 52.04, 64.23, 64.60, 69.35, 70.99, 128.42, 128.56, 128.75, 128.99, 129.19, 129.34, 130.79, 136.47, 136.70, 139.81, 167.21, 171.63, 171.83. For a solution synthesis of **3c** starting from Schiff base **1**, see: Receveur, J.-M.; Roumestant, M.-L.; Viallefont, P. *Amino Acids* **1995**, 9, 391-395.
10. Moore, G.; McMaster, D. *Int. J. Peptide Protein Res.* **1978**, *11*, 140-148.