Tetrahedron Letters No. 31, pp 2839 - 2842.
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0040-4039/78/0729-2839$02.00/0

SOLUBLE POLYMERS IN ORGANIC SYNTHESIS: I. PREPARATION OF POLYMER REAGENTS USING POLYETHYLENE GLYCOL WITH TERMINAL AMINO GROUPS AS POLYMERIC COMPONENT

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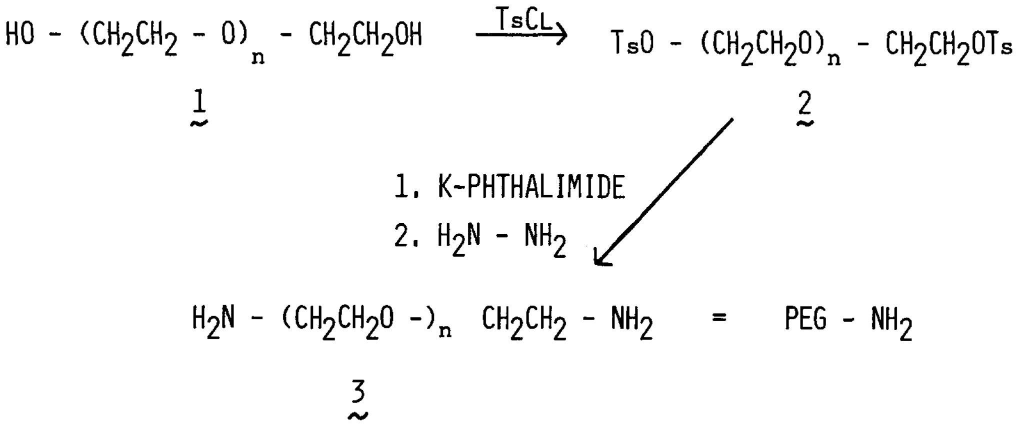
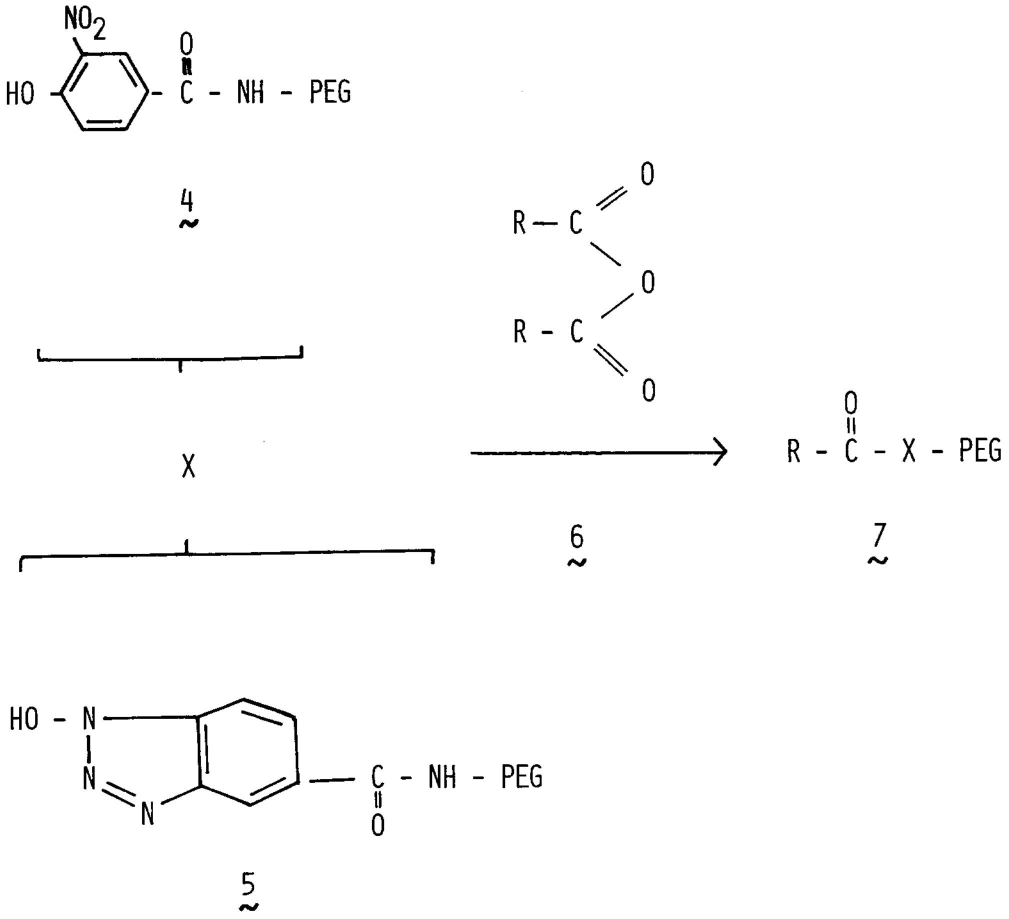
(Received in UK 15 May 1978; accepted for publication 2 June 1978)

A number of polymer reagents have been described for the simplification of organic synthesis (1-5). Most notably, reagents bound to crosslinked polystyrene were successfully applied for peptide synthesis (3,6,7). Investigations upon reaction rates and kinetic course in solid-phase synthesis showed that heterogeneous reactions are subject to steric effects within the solid matrix (8). Furthermore, the preparation and accessibility of insoluble polymer reagents appears to limit a more general application of these compounds. Soluble polymer reagents allow reaction in homogeneous solution and should overcome these deficiencies. As polymeric group, we propose polyethylene glycol (PEG) of Mw 2 000 - 20 000 and its derivatives which have proved very effective in Liquid-Phase peptide synthesis (8,9). The linear chain molecule exhibits favourable physico-chemical properties (8,10) and allows easy separation from compounds not covalently attached to its chain ends. In this paper, we describe firstly a procedure to convert the terminal hydroxylic groups of PEG to the more reactive primary amino groups ($PEG-NH_2$) and secondly the preparation of a number of reagents bound to $PEG-NH_2$. The application of these soluble polymer reagents in peptide synthesis is demonstrated in an accompanying paper.



Commercial PEG was converted to "amino-PEG" [PEG-NH_2 = NH_2-$(CH_2CH_2O-)_nCH_2CH_2$-NH_2] as follows: Dry PEG (Mw 4 000) was reacted with excess tosylchloride (TsCl) in CH_2Cl_2 (10 eq, 2 % w/v pyridine, 25°, 12 h) to yield product 2. Subsequent treatment of 2 with K-phthalimide in DMF (3 eq, 120°, 3 h, N_2) and hydrazinolysis of the resulting product in EtOH (10 eq, reflux, 3 h) afforded the PEG-NH_2 (3). Products 1 - 3 were purified by precipitation with ether and recrystallization from EtOH (8). Reagents insoluble in CH_2Cl_2, DMF or warm EtOH were filtered off prior to precipitation of the PEG derivative. The yield of primary amino groups (90 % as determined by titration) was independent of the molecular weight of PEG for n = 50 - 500. PEG-NH_2 exhibits properties similar to PEG (soluble in CH_2Cl_2, DMF, water; insoluble in ether, cold MeOH or EtOH) and was used exclusively as polymeric part for the preparation of soluble polymer reagents.



In a first example, PEG-bound active esters have been prepared. To this end, 3-nitro-4-hydroxybenzoic acid (1.5 eq) was coupled to PEG-NH_2 with DCCI (1.5 eq) in CH_2Cl_2 to yield product **4**. Active carboxylic esters **7** were obtained by reacting **4** with excess of carboxylic acid anhydride **6** (e.g. N-protected amino acid anhydrides (11)). The corresponding 1-hydroxybenzotriazol (HOBt) esters were prepared analogously by reacting HOBt-5-carboxylic acid with PEG-NH_2 using DCCI as coupling reagent to yield **5**, and subsequent esterification. Compound **4** and **5** were obtained in quantitative yields refered to starting PEG-NH_2. As seen from Table I, the yields for the attachment of the carboxylic components **6** to the PEG-derivatives **4** respectively **5** are $>$ 80 %; these results indicate, that the yields for the preparation of PEG-bound reagents are considerably higher compared to the corresponding insoluble polymer reagents (7,12). All active PEG esters were readily soluble in CH_2Cl_2, DMF, pyridine or water. They are stable for several weeks when moisture is completely excluded.

Table I:
Yields for the preparation of PEG-bound active esters (**7**).

Starting product	anhydride R (**6**)	eq. excess of **6**	yield of **7** in %
4	BOC-Gly	3	93
4	BOC-Val	4	85
5	Z-Ala	3	90
5	BOC-Val	4	89
5	BOC-Ile	4	81
5	Ac	2	100

In a second example, a PEG-bound carbodiimide has been prepared. To this end, PEG-NH_2, Mw 3 000 was successively reacted with isopropylisocyanate (1.2 eq, CH_2Cl_2, 25^o, 2 h) and TsCl (2 eq, Et_3N, CH_2Cl_2, reflux 4 h) to yield the polymer-bound carbodiimide **8** (IR: 2 110 cm^{-1}; elementary analysis: 1.4 % N). Again, excess reagents were removed by precipitation of the PEG-derivative with ether. As a measure for the content of active carbodiimide bound to PEG, the conversion of carboxylic acids to the anhydrides was used as described by Weinshenker and Shen (1). Treatment of several carboxylic acids with the PEG-carbodiimide indicated an overall yield for the conversion of PEG-NH_2 (3) to **8** of ca. 90 %. As shown in the accompanying paper, the PEG-urea derivative (as obtained after reacting **8** with carboxylic acids) could be recycled several times; a slight decrease in the activity of the carbodiimide was attributed to rearrangement of the active esters to unreactive N-acyl-urea derivatives.

$$\underset{3}{PEG-NH_2} \xrightarrow[\text{2. TsCl, Et}_3\text{N}]{\text{1. i-PrNCO}} \underset{8}{PEG-N=C=N-CH(CH_3)_2}$$

3 8

In conclusion we state, that PEG-NH$_2$ represents a favourable polymer for the attachment of low molecular weight reagents. The accessibility of this new PEG derivative is simple and the preparation of the polymer reagents proceeds in high yields; the removal of compounds not covalently bound to PEG-NH$_2$ is accomplished by making use of the large difference in the physicochemical properties of the two components. The capacity, which is 0.1 - 1.0 mM reagent per gramm polymer for PEG-NH$_2$ of Mw 2 000 - 20 000 can be increased by using blockcopolymers of PEG of low molecular weight and functionalized diisocyanates as described elsewhere (13).

This work was supported by the Deutsche Forschungsgemeinschaft.

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