Tetrahedron Letters No. 32, pp 3281 - 3284, 1972. Pergamon Press. Printed in Great Britain.

POLYMERIC REAGENTS I. SYNTHESIS OF AN INSOLUBLE POLYMERIC CARBODIIMIDE

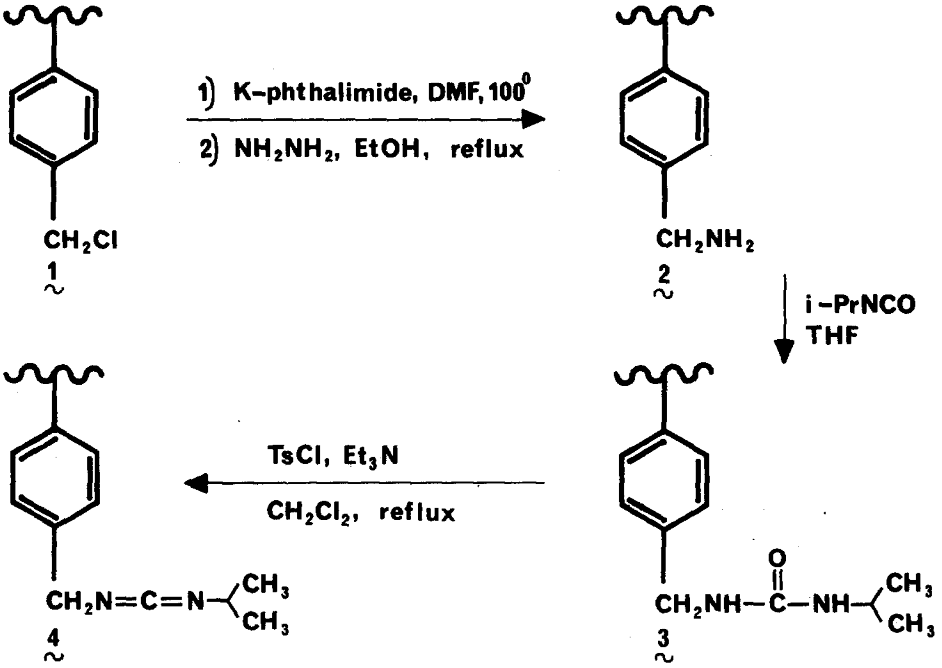
Ned M. Weinshenker and C.-M. Shen[1]
ALZA Research, Palo Alto, California 94304

(Received in USA 10 May 1972; received in UK for publication 30 June 1972)

A major practical problem in organic synthesis is the isolation of the pure reaction product free from contamination due to reagents, solvents and catalysts. The rapid progress being made in new synthetic methods leads one to readily foresee a time when conditions will be found for virtually any type of stereospecific transformation. The isolation step, however, will remain as the most time consuming part of the procedure.

In spite of the success of the Merrifield Synthesis[2] of polypeptides, which has been in use for over a decade, the complementary reagents bound to polymers are only currently receiving attention. Several examples include linear soluble reagents (carbodiimide[3], N-chloroamide[4]) and crosslinked insoluble reagents (N-bromosuccinimide[5], phosphoranes[6] and ligands for metal catalysts[7]). Several carbodiimide derivatives of the usual polystyrene support were mentioned briefly in a report by Fridkin et al.[8]

In our work we have concentrated on crosslinked supports for the reagents. A major consideration is the regeneration of the reagent via a single chemical step after its use in a chemical transformation. This feature will lend versatility to the reagent and might eventually allow for their usage and regeneration on a column similar to ion-exchange resins[9]. The first reagent we chose to study was a carbodiimide[10]. This paper outlines its preparation and reaction with carboxylic acids.



Crosslinked polystyrene beads (Bio-Rad Laboratories, S-X2, 200-400 mesh) were chloromethylated according to the general method of Merrifield[12] yielding a polymer 1 containing 3.1 mmoles Cl/gram (11.05% Cl). Reaction with potassium phthalimide (2.5 eq/Cl, DMF, 100°, 5 hr) followed by hydrazinolysis (hydrazine hydrate, 1 ml/gm polymer in EtOH, reflux 6 hr) produced the primary amine 2. Treatment with isopropylisocyanate (2 eq, THF, 25°, 15 hr) and dehydration of the resulting urea 3 (2 eq TsCl, Et$_3$N, CH$_2$Cl$_2$ reflux 15 hr) afforded the polymeric carbodiimide 4. The infrared spectrum (KBr) displayed strong absorption at 2110 cm^{-1} and elemental analysis (6.8% N) indicated a maximum of 2.42 mmoles of active carbodiimide/gram of polymer. The overall maximum yield for conversion of chloride to carbodiimide (4 steps) was 78 mole %.

The reaction of carboxylic acids with carbodiimide to form anhydrides was used as a measure of the minimum carbodiimide content of the polymer. Unfortunately the side reaction forming N-acyl ureas interferes, but a minimum value for carbodiimide content could be estimated. Conversion of acetic acid to acetic anhydride was followed by gas chromatography (7' x 1/4" Carbowax 20M, 160°) using triglyme as an internal standard. Treatment of polymer **4** (1.0 gm) with an excess of acetic acid in benzene:ether (2:1) yielded 1.4 mmoles of acetic anhydride. Subsequent experiments indicated that some N-acetyl urea was formed and it was assumed that the polymer contained between 1.4 and 2.4 mmoles of available carbodiimide/gram.

Both stearic and glutaric acid were converted to their anhydrides by use of this reagent. Glutaric acid (220 mg) was added to a suspension of 0.99 g of the polymer **4** in 20 ml of 2:1 benzene:ether. After 2 days at room temperature the beads were filtered and the filtrate concentrated to give 195 mg (quantitative) of glutaric anhydride mp 49-51° (commercial sample mp 50°C). Tlc and infrared analysis indicated no trace of glutaric acid. Stearic acid (567 mg) and polymer **4** (1 gm) in 10 ml of 2:1 benzene:ether after 19 hours yielded 360 mg (65%) of crystalline, pure (infrared and mp) stearic anhydride simply by filtration and evaporation of the filtrate.

In several of these experiments the recovered polymer could be easily recycled to the carbodiimide form; however, the activity was generally less than the starting material due to blockage of some active sites by the N-acyl urea rearrangement product.

In an accompanying paper the usefulness of this reagent in the Moffatt oxidation is explored. Work on peptide coupling is presently in progress.

References

1) ALZA Postdoctoral Fellow 1971-72.

2) G. R. Marshall and R. B. Merrifield in "Biochemical Aspects of Reactions on Solid Supports," (G. R. Stark, ed.), p. 111. Academic Press, New York, 1971.

3) Y. Wolman, S. Kivity and M. Frankel, Chem. Communications, 629 (1967).

4) H. Schuttenberg and R. C. Schulz, Angew. Chem. Internat. Edit., 10, 856 (1971).

5) C. Yaroslovsky, A. Patchornik and E. Katchalski, Tetrahedron Letters, 3629 (1970).

6) F. Camps, J. Castells, J. Font and F. Vela, Tetrahedron Letters, 1715 (1971); S. V. McKinley and J. W. Rakshys, jun., Chem. Communications, 134 (1972).

7) R. H. Grubbs and L. C. Kroll, J. Amer. Chem. Soc., 93, 3062 (1971); M. Capka, P. Svoboda, Mr. Cerny and J. Hetfleje, Tetrahedron Letters, 4787 (1971).

8) M. Fridkin, A. Patchornik and E. Katchalski, Peptides, Proc. Eur. Symp., 10th, 1969, p. 166.

9) Ion exchange resins are actually the simplest examples of polymeric reagents and should be so recognized.

10) We chose the carbodiimide moiety for several reasons: 1. ease of preparation; 2. versatility in various types of organic syntheses[11]; 3. the difficulty in many cases of removing the usual urea by-product.

11) See for examples: "Reagents for Organic Synthesis," Fieser and Fieser, John Wiley and Sons, Inc., 1967, pp. 231-235.

12) R. B. Merrifield, Biochem., 3, 1385 (1964).