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POLYMER BOUND EDC (P-EDC): A CONVENIENT REAGENT FOR FORMATION OF AN AMIDE BOND

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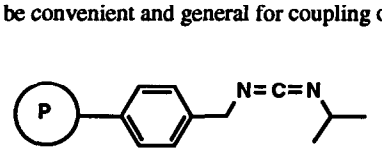
Abstract: A facile preparation of polymer bound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (P-EDC) from commercially available starting materials is described. The P-EDC was found to be a convenient and general reagent for coupling of a variety of amines with diverse carboxylic acids.

As distinct from the reagents simply dispersed, adsorbed or intercalated in inorganic polymers, the covalently linked regents to an insoluble organic polymer have come to acquire importance since the introduction of the solid-phase technique for the synthesis of peptides by Merrifield in 1963.[1] One of the benefits of polymer bound reagents is that work-up of the reaction can be reduced to simple filtration.[2] The successful use of polymer tethered reagents for formation of the amide bond in a "reverse" Merrifield sense has been explored. Several agents such as polymer linked nitrophenol derivatives,[3] polystyrene-attached 1-hydroxy-2-pyrrolidinone[4], polymer coupled 8-acyloxyquinoline[5], a polymer carrying the N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline functional group (poly-EEDQ),[6] polymer attached triphenylphosphine[7] and polymeric carbodiimide 1[8,9] have been prepared and examined for synthesis of various short peptides. The value of carbodiimide based reagents in coupling of an amine with a carboxylic acid stems from facile execution. We became interested in investigating the coupling properties of 1;[10] several difficulties, some of them technical, are associated with 1: (1) its synthesis requires a multi-step sequence from the chloromethylated polymeric beads; (2) it is difficult to determine the content of the active carbodiimide group on the polymer which is generated by a two step sequence from the corresponding urea by dehydration. We now report preparation of polymer tethered 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2, P-EDC) from commercially available starting materials; the reagent was found to be convenient and general for coupling of an amine with a carboxylic acid.



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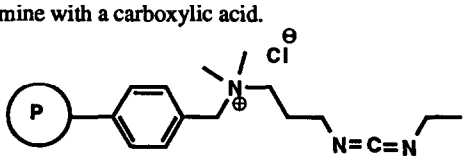


2 (P-EDC)

Over the years, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) has emerged as the reagent of choice for amide coupling reactions, since the basic handle enables the urea and N-acyl urea, if any, to be separated from the products by extraction into an acidic aqueous phase.[11] We decreed that the aqueous work-up can be avoided by attaching EDC to a polymer; we desired to bind EDC on chloromethylated polystyrene-divinylbenzene resin *via* alkylation by taking advantage of the nucleophilic property of the dimethylamino group of EDC. The polymer bound EDC **2** (P-EDC), thus obtained, would behave similar to EDC in solution, but the by-products of the reaction would remain on the polymer. The product, therefore, can be isolated simply by filtration and evaporation of the filtrate. Typically P-EDC is prepared by heating EDC (1.5 equiv.) with chloromethylated polystyrene-divinylbenzene resin in dimethylformamide (DMF, 100° C) or acetonitrile (reflux) for 15 hrs; the long reaction time and the use of 50% excess of EDC are preferred to ensure that all accessible chloromethyl groups are consumed in the quarternization.

The suitability of the chloromethylated polystyrene-divinylbenzene polymer depends on several factors: (1) the pore channel structure of the polymer (1 or 2% cross linking); (2) the density of the chloromethyl groups on the polymer (which varies from 0.8 to 4.5 meq. of Cl/gm). After several experimentation, the reagent with the best coupling properties was obtained from chloromethylated polystyrene-divinylbenzene 2% resin (200-400 mesh, 0.8 meq Cl/gm).[12] The reagent derived from resin with higher meq. of Cl/gm resulted in reduced swelling in chloroform with a detrimental effect on the coupling reaction.

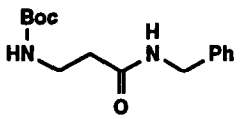
Treatment of a variety of amines (0.2 mmole) with carboxylic acids (0.24 mmole) in chloroform at room temperature with P-EDC afforded a single coupled product. Upon completion of the reaction the product is isolated simply by filtration and rinsing with chloroform; evaporation of chloroform left behind the pure product. The reagent was evaluated for preparation of **3-12** (Table 1) from the corresponding amines and carboxylic acids; the results have been uniformly good. Several observations are worth mentioning: (1) the choice of chloroform as solvent is critical since the use of solvents such as ether or THF slowed down the reaction considerably due to the lack of swelling of the reagent; (2) the excess carboxylic acid remains on the polymer presumably by attaching to EDC; (3) the reagent can be stored at 0°C for months without loss of activity; (4) *tert*-butanol up to 25% can be used as co-solvent to solublize either amine or carboxylic acid; (5) the reaction, for convenience, can be performed in a syringe fitted with a frit and lure lock (or pressure activated check valve); after completion of the reaction, the lure lock is opened, and the syringe is pressurized to filter off the product (Fig. 1); [13] (6) an additional equivalent of a carboxylic acid is required in the coupling of an amine with a basic *tert* nitrogen atom (example **11**); and (7) an unprotected alcohol group does not interfere in the coupling reaction (example **12**).

Preparation of P-EDC. To a stirred solution of EDC (15.7 g, 100.9 mmole) in DMF (800 mL) was added chloromethylated polystyrene-divinylbenzene 2% resin (105 gm, 84 meq. of Cl; 200-400 mesh, 0.8 meq. Cl/gm).[14] After stirring at 100°C overnight, the mixture was cooled and filtered. The polymer beads were washed (200 mL x 3) each with DMF, THF and ether and dried (P_2O_5) under reduced pressure giving 117.9 gms of P-EDC.

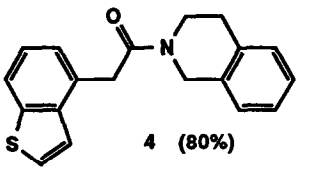
General procedure for coupling. This is illustrated by the synthesis of **3**. To a suspension of P-EDC (650 mgs, ~0.5 mmole of EDC) in chloroform (4 mL) *N-tert*-Boc-ß-alanine (0.22 mmole) and benzylamine (0.2 mmole) were added. After the reaction was shaken for overnight at room temperature, the mixture was filtered. The resin was washed with chloroform (3 x 3 mL), and the combined filtrate was evaporated to dryness to yield **3** (46 mgs, 82%).

In view of the ease of preparation of **2** from readily available starting materials and the results obtained (Table 1), P-EDC should prove useful for the small scale preparation of amides, especially because of the exceptional ease of work-up.

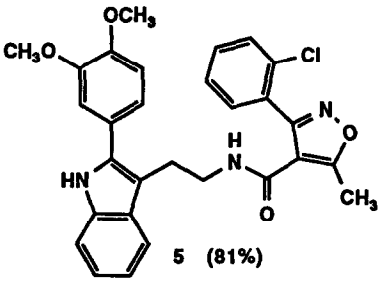
Table 1: Compounds synthesized from the corresponding amines and carboxylic acids using P-EDC.



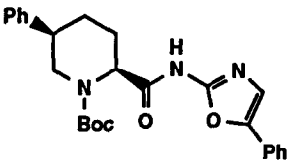
3 (82%)



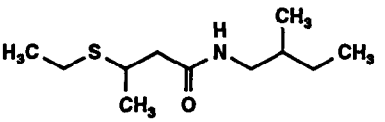
4 (80%)



5 (81%)



6 (83%)



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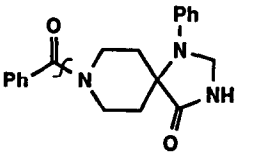
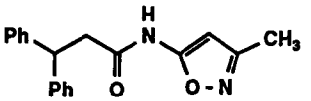
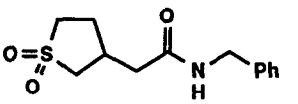


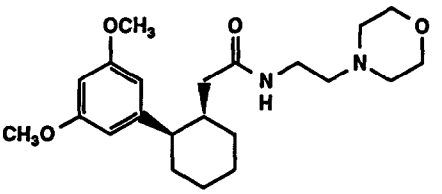
8 (97%)



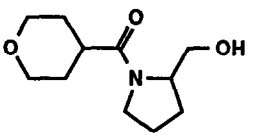
9 (87%)



10 (77%)



11 (quantitative)



12 (72%)

Reference and Notes

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10 Use of **1** for peptide coupling has not been mentioned. We first prepared **1**[9] but to our surprise, it failed to couple *N-tert*-boc-ß-alanine with 3,3-diphenylpropylamine. We are not certain if the lack of success is due to the inferior quality of the reagent; this issue of reliability can be a problem with a multi-step solid phase synthesis. For the use of **1** in the preparation of aldehydes and ketones under Moffat oxidation see: (a) Weinshenker, N. M.; Shen, C. M. *Tetrahedron Letters* **1972**, 3285-3288. (b) Weinshenker, N. M.; Shen, C. M.; Wong, J. Y. *Org. Synth.* **1988**, *Coll. Vol. VI*, 218-219.

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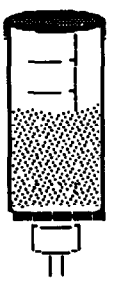
12 Chloromethylated polystyrene resin can be obtained from Peptide International or Fluka Inc.

13 Typical reaction vessel.



14 The commercially available EDC hydrochloride (Fluka Inc.) was free based with aq. potassium carbonate or 10% ammonium hydroxide and extraction of the aqueous phase with methylene chloride.

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