



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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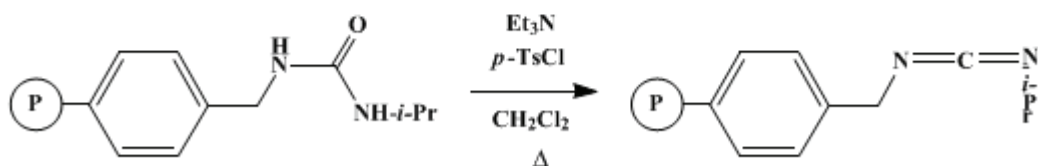
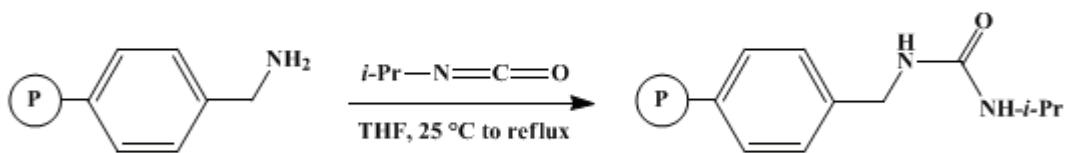
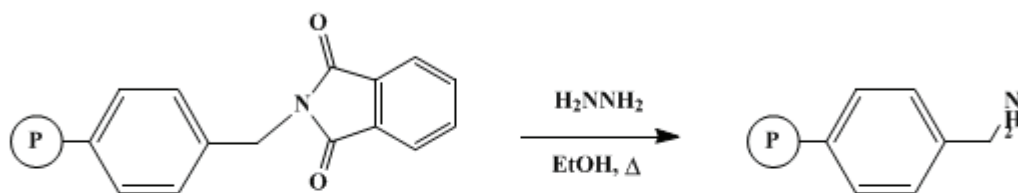
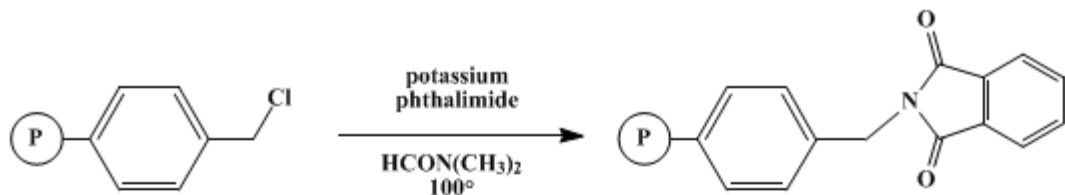
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.951 (1988); Vol. 56, p.95 (1977).

POLYMERIC CARBODIIMIDE. PREPARATION

[Benzene, diethenyl-, polymer with ethenylbenzene, [(((1-methylethyl)imino)methylene]amino)methyl]deriv.]]



(P) = styrene - divinylbenzene copolymer

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Checked by A. Fukuzawa and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Polymeric benzylamine.* A 300-ml., one-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer is charged with 125 ml. of *N,N*-dimethylformamide (Note 1) and 10.0 g. of chloromethylated polystyrene beads (0.0106 mole of active chloride) (Note 2) and (Note 3). A gas-inlet is attached to the top of the condenser, and the system is maintained under a slight positive pressure of nitrogen. The temperature is then raised to 100° with an oil bath, and 2.95 g. (0.0159 mole)

of potassium phthalimide (Note 4) and (Note 5) is added while the mixture is stirred. After stirring at 100° overnight, the mixture is cooled and filtered. The polymer beads are washed with 200 ml. each of distilled water and methanol and dried under reduced pressure, giving 11.70 g. of phthalimido polymer.

The beads prepared above (11.58 g.) are suspended in 175 ml. of boiling absolute ethanol, and 0.94 g. (0.016 mole) of 85% aqueous hydrazine monohydrate is added with stirring. The resulting mixture is refluxed for 10 hours, after which the polymer is collected by filtration and washed with 150-ml. portions of ethanol, aqueous 0.2 N sodium hydroxide, distilled water, and anhydrous methanol. After vacuum drying at 60° for four hours, the yield of polymeric benzylamine is 10.38 g.

B. *Polymeric urea.* A 10.0-g. portion of the benzylamine polymer beads prepared in Part A and 125 ml. of tetrahydrofuran (Note 6) are combined in a 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirrer, a dropping funnel, and a condenser fitted with a gas-inlet tube. A nitrogen atmosphere is established in the system, and the slurry is stirred while 1.35 g. (0.0159 mole) of 2-isocyanatopropane is added. An exothermic reaction ensues and subsides after about 20 minutes. The mixture is then stirred at room temperature for 22 hours, and at reflux for an additional 4 hours. The beads are collected by filtration, washed with 150-ml. portions of tetrahydrofuran (Note 6) and methanol, and dried under reduced pressure over calcium chloride, yielding 9.09 g. of the 2-propyl urea polymer.

C. *Polymeric carbodiimide.* The polymeric urea prepared above (9.09 g.) is combined with 100 ml. of dichloromethane in a 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser fitted with a gas-inlet tube, and a stopper. Under a blanket of nitrogen, 5.76 g. (0.0570 mole) of triethylamine and 2.75 g. (0.0145 mole) of *p*-toluenesulfonyl chloride (Note 7) are added to the stirred reaction mixture. The resulting slurry is refluxed with stirring for 50 hours, cooled to room temperature, and filtered. The polymer beads are washed successively with 100-ml. portions of dichloromethane, ice water, 3:1 dioxane–water, dioxane, and anhydrous diethyl ether. Vacuum drying yields 8.61 g. of polymeric carbodiimide, containing 0.98–1.01 millimoles of carbodiimide per gram (Note 8).

2. Notes

1. *N,N*-Dimethylformamide was dried overnight over Linde type 4A molecular sieves.

2. The checkers used beads of chloromethylated polymer available from Bio. Rad. Laboratories, Richmond, California (Bio Beads S·X2). Chlorine analysis (Note 3) showed that the resin contained 1.06 milliequivalents of chlorine per gram, as specified by the manufacturer.

The submitters prepared the polymer as follows. *Caution! Chloromethyl methyl ether is a carcinogen and is listed as such on the OSHA list. Therefore, preparation of the chloromethylated resin must be performed in a fume hood, the operator must wear gloves, and the reagent must be disposed of in an appropriate manner.* A slurry of 200 g. (1.93 moles) of polystyrene crosslinked with 2% divinylbenzene (Amberlite XE-305, obtained from the Rohm and Haas Company, Philadelphia) and 2.5 l. of chloroform was prepared in a 3-l., three-necked, round-bottomed flask equipped with a dropping funnel, a condenser, and a mechanical stirrer. After stirring for 0.5 hour at room temperature, the mixture was cooled in an ice-water bath, and a mixture of chloromethyl methyl ether (430 ml., 5.69 moles) and anhydrous tin(IV) chloride (45 ml., 0.39 mole) was added dropwise with continuous stirring. After the addition was completed, the ice bath was removed, and the mixture was stirred for an additional 4 hours at room temperature. The beads were collected by filtration and washed successively with 2 l. of 3 : 1 dioxane–water, 2 l. of 3 : 1 dioxane–3 N hydrochloric acid, 1 l. of dioxane, 1 l. of water, and 1 l. of methanol. It is desirable to allow each of the solvents used in the washing procedure to be in contact with the beads for 5–10 minutes before filtration to ensure complete penetration. Drying over calcium chloride under reduced pressure yields 252 g. of the chloromethylated polymer. The chlorine content was 15.50%, equivalent to 4.29 milliequivalents of chlorine per gram of polymer (Note 3).

3. The chlorine content can be determined by either chlorine elemental analysis or a potentiometric titration using a chloride-ion electrode. For titration, about 0.2 g. of polymer is heated in 3 ml. of pyridine at 100° for 2 hours. This suspension is then transferred to a 50-ml. beaker containing 30 ml. of 50% acetic acid and 5 ml. of concentrated nitric acid, and the resulting mixture is titrated against

aqueous 0.1 *N* silver nitrate.

4. All chemicals used were reagent grade unless otherwise specified. A 50% molar excess of reagents was employed throughout the synthesis in order to drive the reactions to completion.

5. Potassium phthalimide was washed with acetone prior to use according to the procedure in *Org. Synth.*, **Coll. Vol. 4**, 810 (1963).

6. Tetrahydrofuran was dried and distilled from lithium aluminum hydride prior to use. For a warning concerning potential hazards of this procedure, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).

7. *p*-Toluenesulfonyl chloride was recrystallized from hexane prior to use.

8. The *maximum* content of active carbodiimide groups can be determined by a nitrogen elemental analysis. The submitters determined the *minimum* carbodiimide content by treating the reagent with excess acetic acid: *ca.* 1 g. of accurately weighed polymeric carbodiimide was suspended in a mixture of 7 ml. of benzene, 3 ml. of ether, and 1.2 g. of acetic acid. After 20 hours of stirring, the conversion to acetic anhydride was determined by GC using a Carbowax 20M column operated at 160°. Triglyme was used as an internal standard. The final, deactivated polymer still showed a very strong absorption at 2140 cm.⁻¹ (KBr) in its IR spectrum. The checkers modified the above procedure slightly by using glutaric acid instead of acetic acid.

3. Discussion

The general procedure described here was originally published by the submitters,² who have used this insoluble reagent to prepare aldehydes and ketones under Moffat oxidation conditions.³ A polymeric reagent offers two advantages: (a) when an oxidation is complete, the urea by-product is cleanly separated from the products by a simple filtration; and (b) the deactivated urea form of the polymer can be recycled efficiently to the carbodiimide form, as outlined in Part C of the present procedure. The use of polyhexamethylenecarbodiimide in peptide syntheses has been mentioned previously.⁴

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 6*, 218

References and Notes

1. Dynapol, 1454 Page Mill Road, Palo Alto, California 94304.
 2. N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett.*, 3281 (1972).
 3. N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett.*, 3285 (1972); N. M. Weinshenker, C. M. Shen, and J. Y. Wong, *Org. Synth.*, **Coll. Vol. 6**, 218 (1988).
 4. Y. Wolman, S. Kivity, and M. Frankel, *Chem. Commun.*, 629 (1967).
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Polymeric urea

Polymeric benzylamine

Polymeric carbodiimide

Benzene, diethenyl-, polymer with ethenylbenzene

[[[(1-methylethyl)imino]methylene]amino]methyl]deriv.]

chloromethylated polystyrene beads

phthalimido polymer

2-propyl urea polymer

chloromethylated polymer

polyhexamethylenecarbodiimide

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

chlorine (7782-50-5)

Potassium Phthalimide (1074-82-4)

urea (57-13-6)

hydrazine monohydrate (7803-57-8)

Glutaric acid (110-94-1)
dichloromethane (75-09-2)
chloromethyl methyl ether (107-30-2)
chloride
tin(IV) chloride (7646-78-8)
dioxane (5703-46-8)
benzylamine (100-46-9)
Tetrahydrofuran (109-99-9)
lithium aluminum hydride (16853-85-3)
N,N-dimethylformamide (68-12-2)
hexane (110-54-3)
triethylamine (121-44-8)
carbodiimide
p-Toluenesulfonyl chloride (98-59-9)
divinylbenzene
2-isocyanatopropane (1795-48-8)