

INSOLUBLE RESINS IN ORGANIC SYNTHESSES I.
PREPARATION AND REACTIONS OF POLYMERIC ANHYDRIDES

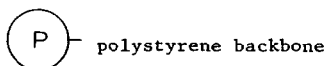
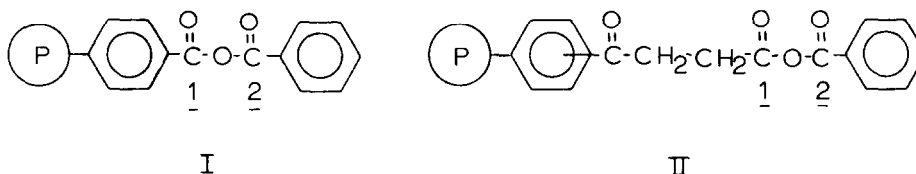
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Recently many workers have pointed out the advantages of utilizing polymeric reagents in organic syntheses^{1,2,3}, a technique similar to the solid phase synthesis of peptides⁴. By employing reactive chemical functions on an insoluble polymer support, the usual purification procedures can be avoided. The excess reagent and other reaction products can be removed by simple filtration so that the desired reaction product alone is left in the filtrate in an ideal case. The simplicity of operation, quantitative yields (as an excess of the reagents may be employed) and mild reaction conditions are of great importance in the derivatization of complex molecules of biological importance and in the synthesis of radiolabelled compounds.

In our preliminary studies we have chosen the acylation of alcohols and amines as a model reaction to be performed by the polymeric reagents. As anhydrides are commonly used as acylating reagents, here we report the preparation of benzoic anhydrides (I and II) on



polystyrene and their reactions with ethanol and aniline.

"Popcorn" polystyrene⁵ was chosen as the insoluble polymeric support. Polymer I was prepared from the polystyrene bearing carboxylic acid functions obtained by the copolymerization of 40.0 g styrene, 0.15 g divinylbenzene and 5.0 g p-vinylbenzoic acid according to the procedure described by Letsinger, *et al.*⁵ The carboxylic acid functions (0.73 meq per gram of the polymer) were converted to the acid chloride by treatment with excess oxalyl chloride in benzene⁶. After washing with hot benzene, the product (5.0 g) was treated with 1 ml pyridine in 50 ml benzene followed by a solution of benzoic acid in benzene (1.0 g in 20 ml). After maintaining at 50° for 2 hr, the polymer was washed repeatedly with hot benzene and the suspended particles of pyridine hydrochloride were removed⁸. The structure of the final product I (5.3 g) was confirmed by its ir spectrum (no bands at 3700-3350 cm⁻¹, carbonyl bands at 1750 and 1710 cm⁻¹). Polymer II was prepared from the succinylated polystyrene (polystyrene bearing -COCH₂CH₂COOH groups). The latter was obtained by the reaction of succinic anhydride on "popcorn" polystyrene in the presence of aluminum chloride according to the procedure described by Yip and Tsou⁹. The carboxylic acid functions (0.9 meq per gram; 5.0 g polymer) were converted to the anhydride by the procedure described above (5.35 g product, ir - no bands at 3700-3350 cm⁻¹, additional bands at 1750 and 1715 cm⁻¹).

The reactions of the polymeric anhydrides were carried out by refluxing 5.0 g polymer with 1 ml aniline (or ethanol) in 50 ml toluene for 1 hr. After removal of the polymer beads by filtration, the solution was carefully distilled (8" Vigraux column) to remove most of the solvent. The residue was then dissolved in chloroform and extracted with sodium bicarbonate solution to remove any benzoic acid. The acid was subsequently precipitated by the addition of hydrochloric acid and isolated by the extraction with benzene. The chloroform solution was then extracted with dilute hydrochloric acid to remove unreacted aniline and benzanilide (ethyl benzoate when ethanol was employed) was obtained by the removal of chloroform. The results are summarized below:

Polymer ¹⁰	Total benzoic ¹¹ acid on 5.0 g polymer	Product with aniline	Product with ethanol	% Anhydride functions re- acted in 1 hr
I	0.35	benzanilide	ethyl benzoate	90%
II	0.4	benzoic acid	benzoic acid	85%

Two products can be formed by the reaction of I or II with the nucleophile (aniline or ethanol). An attack at carbonyl 1 would give rise to benzoic acid, an undesirable product, while an attack at carbonyl 2 would result in the formation of the desired product (amide or ester). We were able to isolate and identify only one product in each case. Anhydride I was effective in carrying out benzylation while anhydride II gave only benzoic acid.

The selectivity exhibited by the anhydride II is not totally unexpected. Benton and Perry¹² have shown that the hydrolysis of acetic benzoic anhydride by water enriched in ¹⁸O results in the incorporation of ¹⁸O in acetic acid. The authors have suggested an A-2 mechanism for the reaction, the acetyl-oxygen bond being broken in both acid and neutral hydrolysis. As the anhydride II is a similar mixed anhydride, an attack at the aliphatic carbonyl is to be expected.

As the anhydride I is structurally similar to benzoic anhydride, the electronic effects alone cannot explain the selectivity of the attack at the carbonyl 2. In our opinion, the proximity of carbonyl 1 to the polystyrene backbone makes the approach of the large nucleophiles more difficult.

At the present we are exploring the possibilities of carrying out the acylations under milder conditions. The potential of these resins in the preparation of mixed anhydrides is also under investigation.

References

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4. R. B. Merrifield, ibid., 85, 2149 (1963).
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8. No attempts were made to remove all traces of pyridine hydrochloride.
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10. Polymer beads of 40-100 mesh size were used in the reactions.
11. This is the amount isolated from the polymer after refluxing the beads with excess potassium hydroxide in dioxane-water (5:1) for 4 hours.
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