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J. A. Moore[a]; J. J. Kennedy[a]
[a] Department of Chemistry, Rensselaer Polytechnic Institute Troy, New York

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Approaches to an Yneamine Resin as a General-Purpose Condensing Agent

J. A. MOORE and J. J. KENNEDY

Department of Chemistry
Rensselaer Polytechnic Institute
Troy, New York 12181

ABSTRACT

The synthetic utility and shortcomings of resins which activate carboxyl groups to form anhydrides, esters, or amides such as polycarbodiimide resins and poly-EEDQ resins are examined. The use of a polymer-bound yneamine function for such purposes is proposed, and synthetic approaches to this goal are described. Tentative evidence for the existence of a stable intermediate in the reaction of an insoluble yneamine with benzoic acid is also presented.

The general class of polymeric reagents has been divided [1] into three types of reactions shown in Eqs. (1). Type A reagents are exemplified by the Merrifield technique of peptide synthesis [2] in which appropriately blocked amino acids (M_x) are attached to the resin P, one at a time with intermediate washings. The peptide remains bonded to the resin until the end of the synthesis when it is released and isolated. Type B reagents are typified by "active" ester polymers, such as a nitrophenol resin [3], in which a carboxyl group of acid M_1 is activated by being bound to P as a nitrophenyl ester and then displaced from the resin by reaction with a nucleophile, M_2.

Type A:

$$P + M_1 \longrightarrow P\text{–}M_1 + M_2 \longrightarrow P\text{–}M_1\text{–}M_2$$

Merrifield Synthesis

Type B:

$$P + M_1 \longrightarrow P\text{–}M_1 + M_2 \longrightarrow P + M_1\text{–}M_2$$

"active" ester polymers

Type C:

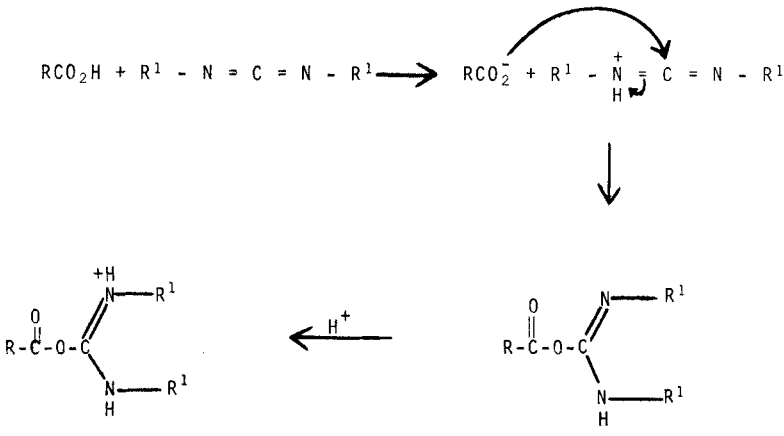
$$P + M_1 + M_2 \longrightarrow P' + M_1\text{–}M_2 \qquad (1)$$

Type C reagents are the topic of this investigation and represent systems in which the polymer P is sufficiently reactive that species $P\text{–}M_1$ is formed in situ. The polymer conjugate $P\text{–}M_1$ may or may not, in principle, be stable. In practice, the previously reported systems [4-6] are presumably not stable, or at least undergo further reaction rapidly under the conditions used.

Our aim here is to review briefly the work on type C polymers which has been published and then to present data on a new type C resin based upon the chemistry of the yneamine [7] group.

The chemistry of the reaction of a carboxyl group, RCO_2H, with a carbodiimide group is outlined in Eqs. (2) and (3). The carbodiimide molecule is protonated and then attacked by the carboxylic acid to form an O-acyl urea which is protonated by a second molecule of carboxylic acid [Eq. (2)]. The protonated O-acyl urea may undergo a number of reactions [Eq. (3)]. It has been shown [8, 9] that, under the conditions of Merrifield Synthesis, path b is essentially the only operative pathway which leads to product. Thus if the carbodiimide functionality were to be incorporated into a polymer, the species $P\text{–}M_1$ would very rapidly be converted to P and a low molecular weight anhydride which would then react with available nucleophiles. Thus the intermediate which undergoes nucleophilic attack is, e. g., in peptide synthesis, an amino acid anhydride resulting in activation of only half of the free carboxyl groups present under stoichiometric reaction conditions.

A reaction competing with product formation is path c, a rearrangement of O-acyl to N-acyl urea [10]. This material is a "dead-end" in the reaction sequence because it has been shown not to undergo reaction d [11]. This side reaction is of greater significance for a regenerable polymeric reagent because it will mean that ultimately all



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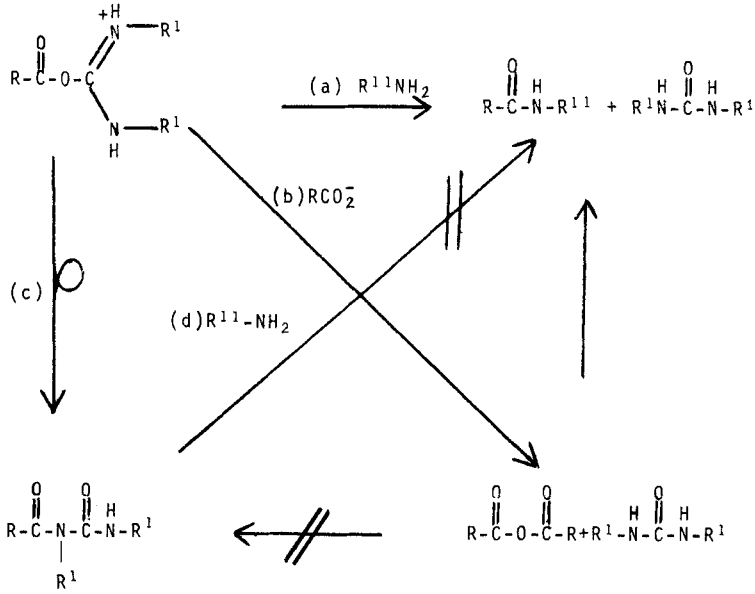
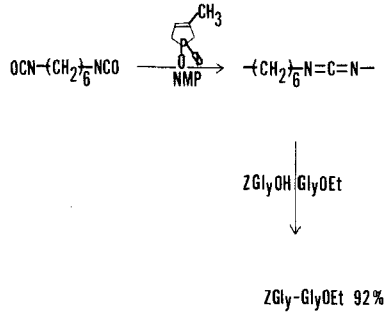


(3)

carbodiimide groups will be converted to N-acyl urea functions which will no longer be regenerable.

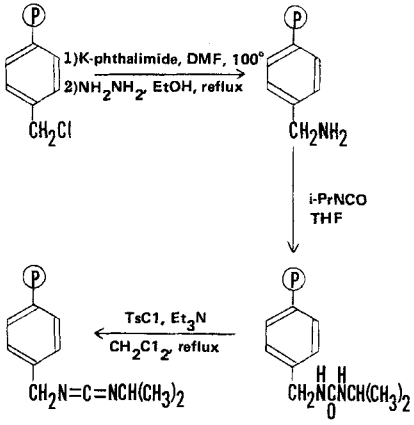
The first example of a polymeric carbodiimide reagent which has been reported involved conversion of a diisocyanate to a polymeric carbodiimide, in which the carbodiimide function constitutes part of the chain backbone [4] [Eq. (4)]. Treatment of hexamethylene



(4)

diisocyanate with a phospholene oxide yielded poly(hexamethylene carbodiimide). This material was treated with ethanol to block terminal isocyanate groups, filtered, ground, and extracted with boiling methylene chloride. The insoluble product was treated with acetyl-N-hydroxysuccinimide to acylate any free amino groups which might have been formed. A typical example of peptide formation used 20 mmole of resin suspended in CH_2Cl_2 and 2.5 mmole each of ZGlyOH, HCl·GlyOEt, and Et_3N with stirring for 12 hr. The dipeptide was obtained in 92% yield as a crystalline solid. Similar yields were obtained with optically active amino acids but no measure of the extent of racemization was made. Such a resin has, in principle, 2.7 meg of –N=C=N– per gram of resin but no assessment of the resin's total reactive capacity was made. Further, no attempts to regenerate this material from its final polyurea form were reported. The generally poor solubility behavior of most polyureas would probably interfere with attempts at regeneration.

The first system which utilized the chemistry of carbodiimides in a regenerable system was reported by Weinshenker and Shen, [5] [Eq. (5)]. Chloromethylated polystyrene resin was converted to carbodiimide functionalized resin in 78% overall yield by amination (via the Gabriel Synthesis), reaction with isopropyl isocyanate, and then treatment with tosyl chloride and triethyl amine. Stearic anhydride was prepared in 65% yield from stearic acid by refluxing the acid in the presence of the resin in 2:1 benzene:ether. Oxidation of

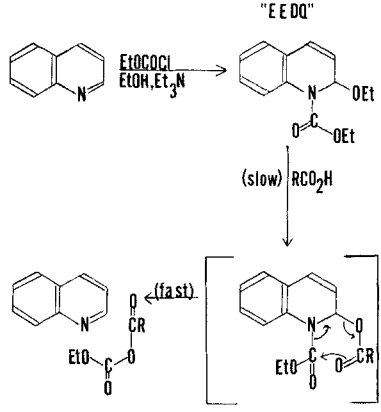


(5)

a range of alcohols, including a labile prostaglandin intermediate, in a Pfitzner-Moffat reaction was accomplished in yields ranging from 67-91%.

A similar resin (ethyl isocyanate was used instead of isopropyl) [12] has been reported and used for peptide synthesis. A 1-g portion of this resin produced 0.43 mmole of (2,4-dinitrophenylthio)-Gly-L-Val OMe when reacted with a mixture of Dnps-Gly and L-Val-OMe in CH_2Cl_2 for 16 hr. No measure of the tendency of the polymeric carbodiimide group to cause racemization has been, to our knowledge reported.

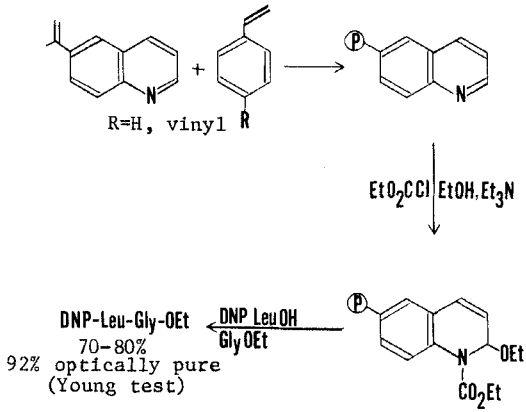
The chemistry of the reaction of EEDQ (formed from quinoline, ethanol and ethylchloroformate) is outlined in Eq. (6) [13]. The



(6)

intermediate formed upon reacting a carboxylic acid with EEDQ is reported to be so labile that it has never been isolated, even from reactions performed at low temperatures. The mixed anhydride which is formed is then attacked by the nucleophillic species which are present.

Brown and Williams [6] have reported the incorporation of the EEDQ group into a crosslinked resin by copolymerization of 6-isopropenylquinoline with styrene and divinylbenzene (2:3.08 parts by weight) [Eq. (7)]. After purification by exhaustive extraction the resin was

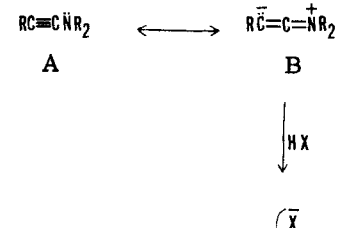


(7)

found to contain 1.33 mmole of nitrogen (as N_2) per gram of resin. The quinoline form of the resin was converted to active reagent by overnight reaction in methylene chloride (6 ml/g) with a slight excess of ethyl chloroformate, ethanol, and triethyl amine. The resin could be stored in this form for at least three months, if protected from moisture. The amount of reactive functionality formed in this way was assayed by reacting an excess of N^{α}-DNP-L-leucine and glycine ethyl ester with the resin and determining the amount of N^{α}-DNP-L-Leu-GlyOEt formed by spectrophotometry. In this way the resin was found to produce 0.2 mole of this dipeptide per gram of resin. Monomeric EEDQ gave a dipeptide which was racemized to the extent of 5.0 ± 0.1%. The resin caused 8.1 ± 0.7% racemization. The same reaction when performed using dicyclohexyl carbodiimide in the presence of two equivalents of N-hydroxysuccinimide showed 8.9 ± 0.1% racemization. The polymeric reagent seems to be slightly less effective (with respect to racemization) than simple EEDQ but is at least comparable in this regard to the widely-used DCC/HOSu combination. The regenerability of the resin was borne out because the same 5 g sample of polymer was used for the racemization tests and all preparative reactions and was regenerated several times.

Surprisingly, no rationale for the enhanced racemization caused by the resin was presented. We may speculate that unconverted quinoline groups may have taken part in the racemization process in some way.

The chemistry of the yneamine functionality is outlined in Eqs. (8) and (9) [7]. The interaction of the amino group with the directly-linked multiple bond chemically activates the molecule. Qualitatively,



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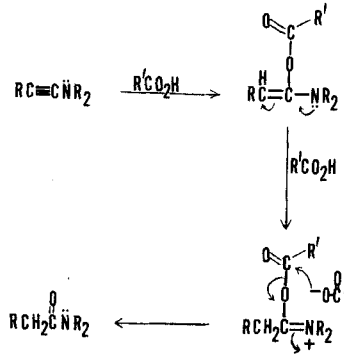


(9)

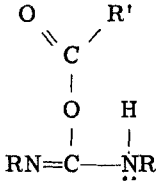
the chemistry of yneamines can be discussed on the basis of two resonance structures, A and B. It appears (experimentally) that the ketene-iminium structure is of predominant importance in the reactivity of this group. Yneamines behave well as nucleophiles, adding protons exclusively in the β position and the anions X^- [Eq. (8)] of acids, alcohols, water, and the negative ends of polar bonds in the α position. Nucleophilic amine additions to yneamines proceed best under acid catalysis, which is consistent with the view that they add to the ketene-iminium structure. Thus acid-catalyzed hydration of yneamines

yields amides, as does any reaction in which the overall process is dehydration [Eq. (10)]

$$R\text{–}C{\equiv}C\text{–}NR_2 \xrightarrow{H_2O/H^+} RCH_2\text{–}\overset{\overset{O}{\|}}{C}\text{–}NR_2 \qquad (10)$$

As dehydrating agents, yneamines react rapidly under mild conditions and, from experimental observation, are not subject to the O-acyl to N-acyl rearrangement which plagues carbodiimides. In analogy to the chemistry of carbodiimides, Eq. (10) outlines the reaction of a carboxylic acid with an yneamine. Yields of anhydride are greater than 90% (Table 1), and the reaction is usually carried out at or below, room temperature [14].

The species presumed to be a transient intermediate in the reaction of a carbodiimide group with a carboxyl function (I) is compared with the analogous species (II) expected from a similar interaction for an yneamine. The major differences are seen to be that the yneamine-derived intermediate is less polar and more hindered than its carbodiimide-derived counterpart.



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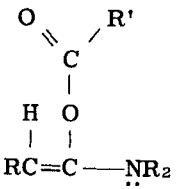


II

Thus, the chemistry of these two groups should show parallel behavior. Indeed, amides and peptides have been synthesized using yneamines. Yields are high (> 90%) (Table 2), and reaction conditions are mild (temperatures range from -20 to 40°C).

Esterifications have been also carried out with yneamines [7] [Eq. (11)].

$$Ph\text{–}OH + HO\overset{\overset{O}{\|}}{C}Ph \xrightarrow[THF(1\ hr)\ 40^\circ C]{Ph\text{–}C{\equiv}C\text{–}CN(Et)_2} Ph\text{–}O\text{–}\overset{\overset{O}{\|}}{C}\text{–}Ph + PhCH_2\text{–}\overset{\overset{O}{\|}}{C}(Et)_2 \quad (87\%) \qquad (11)$$

TABLE 1. Acid Anhydride Formation with Yneamines and Dicyclohexylcarbodiimide

	Acid anhydride formation (%)		
	$C_6H_5C{\equiv}C{-}N(CH_3)_2$	$t\text{-}C_4H_9C{\equiv}C{-}N(CH_3)_2$	$C_6H_{11}{-}N{=}C{=}N{-}C_6H_{11}$
$n{-}C_3H_7COOH$	96	93	70
C_6H_5COOH	98	97	63

TABLE 2. Synthesis of Z-L-Val-L-Val-OCH_3 from Z-L-Val-OH and H-L-Val-OCH_3 in THF at 40°C[a]

Yneamines R–C≡C–R'				
R	R'	Time (hr)	Yield (%)	DL (%)
t-Bu	$(CH_3)_2N$	1	64	0
			50	
		4	80	0
t-Bu	$(C_2H_5)_2N$	1	77.5	0
Ethyl	$(C_2H_5)_2N$	1	87	0
Methyl	$(CH_3)_2N$	1	51	0
H	$(C_2H_5)_2N$	1	25	2.5
Methyl	Piperidino	1	41.5	0
Phenyl	$(CH_3)_2N$	1	79	0
Phenyl	$(C_2H_5)_2N$	1	79.5	0
t-Bu	$C_6H_5(CH_3)N$	1	0	-

[a]Data of Weygand et al. [15].

Generally, yneamines are sufficiently thermally stable that they can be handled normally, as indicated by the example of the commercially available diethylaminomethylacetylene.

From the above given considerations, it may be appreciated that developing methods and procedures for the incorporation of the yneamine functionality into appropriate polymeric matrices represents a goal which may lead to the development of a dehydration reagent of wide applicability to organic synthesis.

The specific aims of this work are: to develop means whereby the yneamine group may be incorporated into commercially available chloromethylated styrene copolymers and to test the efficacy of the yneamine resin as a dehydration agent: (a) with carboxylic acids to form anhydrides, (b) in amide synthesis, (c) in esterification, particularly of sensitive substrates, and (d) in peptide synthesis with emphasis on yield, racemization, and purity.

Yneamines have been synthesized by a variety of methods [7]. However, of particular interest is their synthesis from amides [16, 17] and thioamides [18], as shown in Eqs. (12) and (13).

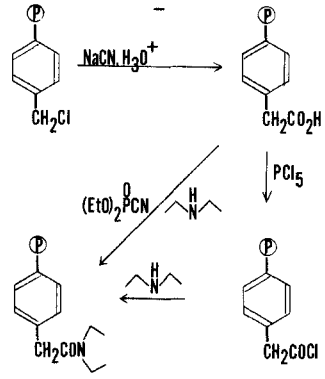
$$RCH_2\overset{O}{\overset{\|}{C}}NR_2 \xrightarrow{COCl_2} (RCH_2C{=}\overset{+}{N}R_2)Cl^- \xrightarrow{Base} RC{\equiv}CNR_2 \quad (12)$$

Cl

$$C_6H_5CH_2\overset{S}{\overset{\|}{C}}NR_2 \xrightarrow[-H_2S]{NaNH_2/xylene} PhC{\equiv}CNR_2 \quad (13)$$

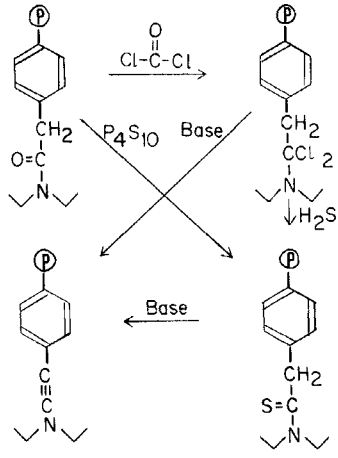
In both cases, overall yields are high, > 70%.

Application of these methods to the proposed resin are shown in Eqs. (14) and (15). All these reactions were first carried out on



(14)

appropriate model compounds so that authentic samples would be on hand. All the indicated benzylic compounds were obtained by standard methods in yields of at least 60-79%. However, when we attempted to transfer these reactions we were less successful. Using commercially available chloromethylated polystyrene beads from Biorad we were able to displace the reactive chloride completely by cyanide by treating the resin with 1.1 equivalent of NaCN in dimethylformamide at 100°C for 2 days. Pilot experiments on the hydrolysis of the nitrile seemed to indicate that we were encountering difficulties which might be attributed to contamination of the resin with suspending agents used in the manufacture of the beads. We had a supply of Dow experimental chloromethyl styrene monomer (XD-1915L, 60:40 meta: para mixture), and we therefore decided to prepare the necessary monomers up to the stage of vinyl phenylacetamide and then fabricate soluble and insoluble polymers.

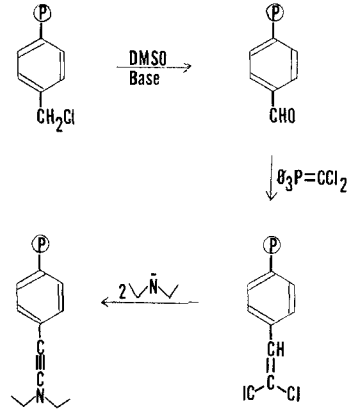


(15)

The conversion of chloromethyl styrene to the nitrile [19], the acid, and the acid chloride [20] are all described in the literature. The first three steps proceeded well but the amidation was better accomplished using diethylphosphoryl cyanide [21] directly on the acid. The previously undescribed N,N-diethylvinylphenylacetamide was copolymerized with styrene to give soluble copolymers ranging from 0% amide through the homopolyvinylphenylacetamide. When a soluble copolymer was subjected to any of the reaction sequences shown in Eq. (15), crosslinked insoluble materials were obtained which showed only weak infrared absorptions in the region characteristic of N–C≡C. The harsh conditions ($NaNH_2$, refluxing xylene) found necessary for the model compounds are clearly unsuitable for the polymeric system.

We therefore turned to a bit more exotic and highly effective set of reactions as outlined in Eq. (16). Kornblum oxidation of crosslinked (2%) chloromethyl polystyrene [22] yielded a completely formylated resin. When this material was treated with dichloromethylene triphenyl phosphorane (generated in situ) [23], vinylidine chloride groups were introduced into the polymer in about 87% yield (elemental analysis for chlorine). Treatment of the vinylidinated resin with two equivalents of lithium diethylamide in tetrahydrofuran yielded a resin which contains approximately 58% of yneamine groups (elemental analysis for nitrogen) and which shows an intense IR absorption at 2180 cm^{-1}.

The stoichiometric reaction to be expected when the yneamine resin is reacted with a carboxylic acid is shown in Eq. (17). Thus, 1 mole of yneamine group should combine with 2 moles of carboxylic acid to yield 1 mole of anhydride and 1 mole of amide resin. What



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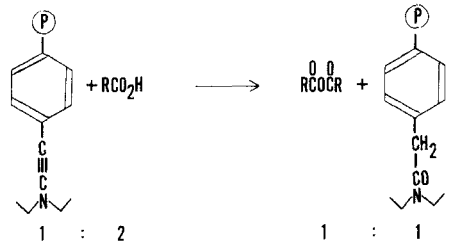

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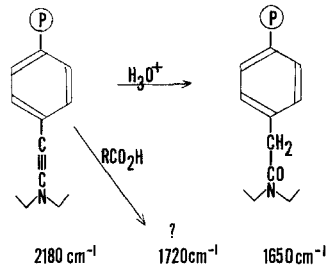
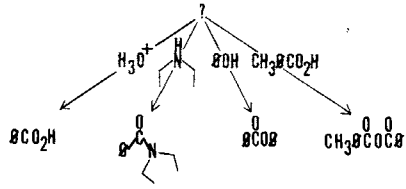


(18)

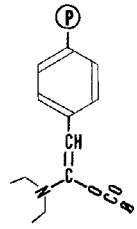
was actually found when the resin was treated with a carboxylic acid is shown in Eq. (18). Variable, but low yields of anhydride were sometimes produced, but more often no appreciable amount of product was obtained. Treatment of the resin with aqueous acid resulted in a shift of the major IR absorption at 2180 cm^{-1} to that of the amide at 1650 cm^{-1}. When the resin was treated with less than equivalent amounts of benzoic acid, a new absorption appeared at 1720 cm^{-1}.



(19)

The chemical behavior of the species absorbing at 1720^{-1} is delineated in Eqs. (19). The resin was washed with CH_2Cl_2 after treatment with benzoic acid until no organic material was found in the extract and then treated with aqueous acid to yield benzoic acid. Treatment with diethylamine yielded diethyl benzamide, and phenol was converted to phenylbenzoate. When toluic acid was added to the resin, the mixed anhydride of benzoic and toluic acids was obtained. All of these products were shown to be identical to authentic samples prepared by standard methods.

Considering these results, we are brought to the conclusion that the mode of action of the yneamine group is different from that of the carbodiimide group, in that the intermediate formed by addition of a carboxylic acid is stable and probably has the structure III.



III

CONCLUSION

We have developed a sequence whereby we can readily incorporate the yneamine group into commercially available chloromethylated polystyrene.

We have shown the resin so produced to be not only effective as a dehydration agent but also to proceed by a mechanism different from that of carbodiimide, so that: carboxylic acids may be converted to anhydrides and even to mixed anhydrides, amides can be formed, and phenolic esters can be formed.

Our current efforts are directed toward examining the scope of reactivity of the resin, completing our goals (peptide synthesis, esterification of sensitive esters) and to developing efficient reaction pathways for the regeneration of the yneamine functionality.

ACKNOWLEDGMENTS

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