

REGIOSPECIFIC AMINATION OF 3-SUBSTITUTED PYRIDINES USING IMIDOYL CHLORIDE FUNCTIONALIZED POLYSTYRENE

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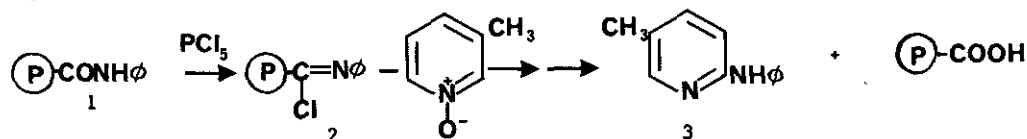
Abstract -New imidoyl chloride functionalized polystyrenes have been prepared and reacted with pyridine 1-oxides; regiospecific acylation of 3-substituted pyridines at the 6-position has been achieved, the corresponding aminopyridine obtained by hydrolysis and, the polymer reagent recycled.

2-Aminopyridine derivatives have important applications in medicine and agriculture [e.g. niflumic acid,^{1a} pyrilamine,^{1b} phenylamidol,^{1c} Alfacon;^{1d} 3,5-bis(trifluoromethyl)pyrido[3,2-d]imidazole is a herbicide,^{1e} and 3-chloro-2-(2,6-dinitro-4-trifluoromethylanilino)-5-trifluoromethylpyridine is a fungicide^{1f}], or for the synthesis of other 2-substituted pyridines. The primary amines are usually prepared by the Tschitchibabin reaction, secondary and tertiary amines from 2-halopyridines and the corresponding amines. When a β -substituted 2-aminopyridine is required the first method gives mixtures of 2,3- and 2,5-disubstituted derivatives, and the halopyridine is sometimes tedious to get for the second method. We developed a procedure for the direct acylation in high yield of heteroaromatic N-oxides using imidoyl chlorides which resulted in a one pot, two-step method of obtaining secondary 2-aminopyridines,² and this method was extended by Wachi and Terada³ to the synthesis of primary 2-aminopyridines. When 3-substituted pyridine 1-oxides were used this still led to mixtures of 2,3- and 2,5-isomers.⁴ We now report the synthesis of imidoyl chloride functionalized polystyrenes and their use in the regiospecific amination of 3-substituted pyridine 1-oxides to yield 3-substituted 6-aminopyridines.

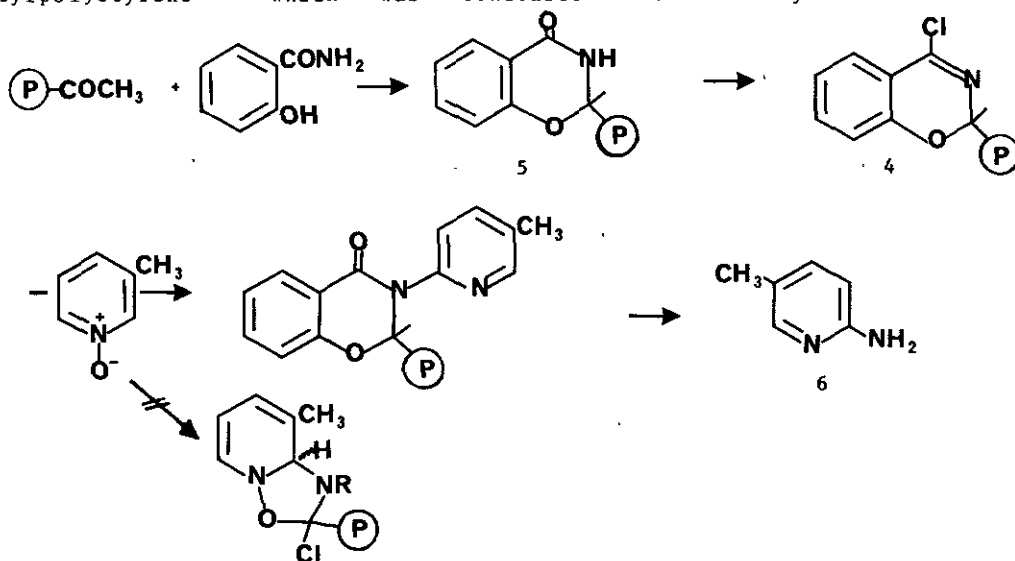
Best results were obtained using macroporous styrene-divinylbenzene copolymer (20-50 mesh, average diameter 800 Å) that had been washed⁵ to remove surface impurities from the polymerization. The N-phenylcarboxamide (1)⁶ [N (found) 3.94%] gave the N-phenylimidoyl chloride polymer (2) (PCl₅, CCl₄, reflux, 24 h) (2.51 meq of Cl/g; 89.3% completion) ir (KBr) 1655 cm⁻¹ (C=N). In contrast to the case with

small molecules, no imidoyl chloride was formed with thionyl chloride or $\text{Ph}_3\text{P}/\text{CCl}_4$. Reaction with pyridine 1-oxide (2 eq.) was carried out by heating in ethylene chloride solution with the imidoyl chloride polymer (1 eq.) for 24 h and filtering the polymer; [ir 1660 cm^{-1} (amide $\text{C}=\text{O}$); 0.42 meq. of Cl/g (83.3% completion)]. Hydrolysis in boiling 10% aq. HCl for 20 h, filtration of the carboxypolymer (3.35 meq. of $\text{CO}_2\text{H}/\text{g}$; ir $3400\text{--}3000$, 1700 cm^{-1}), basifying the filtrate and extracting with ether gave 2-anilinopyridine: mp $106\text{--}108^\circ\text{C}$ (48%), identical with an authentic sample. The polymer was recycled twice, the yield of 2-anilinopyridine being 37.3% on the third run.

The reaction of 3-picoline 1-oxide with *N*-phenylbenzimidoyl chloride gave a mixture of 2- and 6-acylaminated products in the ratio of 1:12 (total yield 48%).⁴ Chromatographic separation was necessary to resolve the products and to separate the benzanilide formed. On the other hand, acylation of 3-picoline 1-oxide using the imidoyl chloride polymer (2) followed by work up as above gave 2-anilino-5-methylpyridines (3) (40.2%) exclusively, identical with authentic sample and recovered $\text{P-CO}_2\text{H}$ which, again, was recycled twice with only a slight decrease in the yield of desired product.

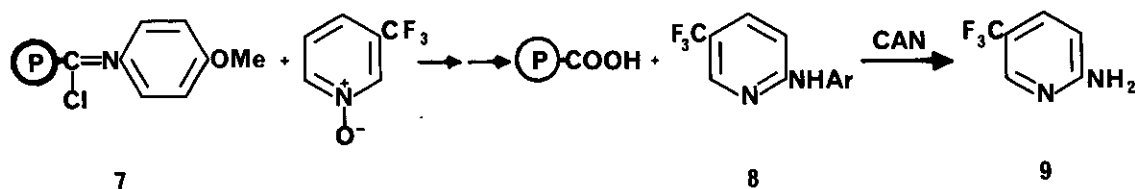


The 4-chloro-2-methyl-1,3-benzoxazin-2-yl polystyrene (4) was prepared from acetylpolystyrene^{7,8} which was condensed with salicylamide in boiling



chlorobenzene in the presence of MgSO_4 while anhydrous HCl was bubbled through,⁹ to give the benzoxazinone (5). The imidoyl chloride 4 was obtained using $\text{PCl}_5/\text{CCl}_4$ (60 h)(1.68 meq. Cl/g , 47.9% completion from crosslinked polystyrene). Reaction of 4 with pyridine 1-oxide followed by acid hydrolysis gave 2-aminopyridine (44%)¹⁰ together with salicylic acid and recovered acetylpolystyrene (which was recycled twice). When 3-picoline 1-oxide was acylaminated with the non-polymeric imidoyl chloride and the product hydrolyzed a mixture (75.8%) of 2-amino-5-methyl- and 2-amino-3-methylpyridine was obtained in the ratio of 35:1 (resolution by GLC¹¹ was necessary). Amination of 3-picoline using the polymer 4 gave 2-amino-5-methylpyridine (6)(42.9%) exclusively (no trace of the 2,3-isomer was detected by GLC). The lower yield of product in this case is made up by the regiospecificity of the reaction and the ease of work up and recovery of the acetylpolymer, which can be recycled.

3-Trifluoromethylpyridine 1-oxide¹² and *N*-4-methoxyphenylimidoyl chloride polystyrene polymer (7)¹³ in the presence of Et_3N gave 2-(4-methoxyanilino)-5-trifluoromethylpyridine (8)(29.8%): mp 108-108.5°C, and recovered carboxypolymer. This was recycled twice yielding 8 (25%) on the third pass. Amide (8) was oxidized with ceric ammonium nitrate in aq. acetonitrile at 0°C for 1.5 h to give 2-amino-5-trifluoromethylpyridine (9)(54.2%): mp 44-45°C.¹⁴ A somewhat better overall yield (31.6%) of 9 could be obtained more conveniently from 3-trifluoromethylpyridine 1-oxide and imidoyl chloride 4.



Thus, while functionalized polymers give somewhat lower yields than non-polymeric reagents they have the advantage of cleaner, easier work-up, of giving readily recoverable and recyclable polymer and, in the case of 3-substituted pyridines, of regiospecificity of substitution to the least hindered position, presumably because of steric interaction between the very bulky polymer and the substituent in the transition state leading to the more hindered product. We believe this concept will have wider practical applications.¹⁵

REFERENCES AND NOTES

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9. No oxazine was formed in boiling CHCl_3 , CH_2Cl_2 , or C_6H_6 , the usual solvents for such reactions.
10. Wachi and Terada³ reported very high yields of 2-aminopyridine from pyridine 1-oxide and 4-chloro-2,2-dimethyl-1,3-benzoxazine. In the hands of two different coworkers in our laboratories the maximum yield of acylation product obtained in this case was 67%.
11. A column of 5% SE-30 on Gas Chrom Q (3' x 1/8") temperature programmed from 100° to 150°C was used.
12. R. A. Abramovitch and Y.-X. Wang, unpublished results. We thank Dr. T. Haga of Ishihara Sangyo Kaisha for a gift of 3-trifluoromethylpyridine.
13. From the 4-methoxybenzanilide polymer in CH_2Cl_2 (NH), 1660 cm^{-1} (C=O) and $\text{PCl}_5/\text{CCl}_4$ to give imidoyl chloride (1.82 meq. of Cl/g of resin).
14. Identical with an authentic sample kindly supplied by Dr. T. Haga, Ishihara Sangyo Kaisha, Ltd. Shiga, Japan.
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