Tetrahedron Letters No. 21, pp 1823 - 1826, 1973. **Pergamon Press. Printed in Great Britain.**

POLYMER PROTECTED REAGENTS: (II) ESTERIFICATIONS WITH Ⓟ-$AlCl_3$

E.C. Blossey[1], L.M. Turner and D.C. Neckers*[2]
Department of Chemistry, University of New Mexico
Albuquerque, New Mexico 87106

(Received in USA 26 **February** 1973; **received in UK for publication** 3 **April** 1973)

In a recent communication from our laboratories, the advantageous use of a polymer protected reagent, polymer protected anhydrous aluminum chloride (Ⓟ-$AlCl_3$) was reported.[3,4] This polymer protected reagent, a tightly bound complex between anhydrous aluminum chloride and polystyrene-divinylbenzene copolymer beads, was described as a polymer protected dehydrating agent which could be released from the polymer by placing it in appropriate swelling solvents.

As part of a general program designed to investigate reactions of polymer protected anhydrous reagents, we report studies of Ⓟ-$AlCl_3$[5] as a mild catalyst for esterification. Ⓟ-$AlCl_3$ combines the advantages of being both a Lewis acid and a dehydrating agent and therefore is ideal for condensation reactions in which very mild conditions are required.

As an example, n-butyl propionate was prepared from propionic acid (0.02 mole) and n-butanol (0.04 mole) by stirring the reagents at room temperature for 46 hrs. with 0.5 g of Ⓟ-$AlCl_3$ in 2.0 ml benzene. After filtering the polymer and removal of the benzene and n-butyl alcohol, n-butyl propionate[6] was isolated in 96.8% yield. A similar experiment carried out with all reagents but Ⓟ-$AlCl_3$ produced only 5.6% of n-butyl propionate under identical conditions.

Similar reactions with various acids and alcohols using Ⓟ-$AlCl_3$ as a catalyst are compared with uncatalyzed reactions in Table I. From these results it is clear that the more sterically hindered alcohols react slowly and electron withdrawing groups at the α-position of carboxylic acids enhance esterification, Table II.

Table I

Product Yields - Esterification Reactions

Acid	Alcohol	Mole Ratio (Acid/alcohol)	T(C°)	Time (hr.)	Yield(%)[a] No Catalyst	Ⓟ-$AlCl_3$
Propionic	1-butanol	1:2	95	1	5.5	56.8
" "	" "	1:2	95	2	11.1	70.0
" "	" "	1:2	25	46	5.6	96.8
Propionic	2-butanol	1:2	95	2	0	36.0
" "	" "	1:2	25	70	0	16.2
Propionic	2-methyl-2-propanol	1:2	95	41	0	0
Acetic	<u>trans</u>-4-<u>t</u>-butylcyclohexanol	1:2	95	26	17.0	35.1
"	" " "	1:2	95	53	38.7	52.5
"	cholesterol	1:1	95	68	3.8	58.0
Cyclopropane carboxylic	1-butanol	1:1	95	18	9.5	56.1
Benzoic	" "	1:1.1	95	5	0.5	22.9
" "	" "	1:1.1	95	46	6.4	44.3
<u>p</u>-Nitrobenzoic	" "	1:1.1	95	42	0	5.5

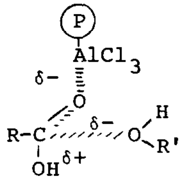
a Yields determined by g.l.c. with an added internal standard

Table II[a]

Acid	Yield, no catalyst[b]	Ⓟ-$AlCl_3$
Acetic	0.0	30%
Adipic	0.0	67%[c]

a All reactions at 25° for 24 hours with 1-butanol in benzene
b Ratio of product (ester) to a specific internal standard by g.l.c.
c Combined total of mono- and diester at 25°

The stereochemistry of the Ⓟ-$AlCl_3$ reactions was shown by use of <u>trans</u>-4-<u>t</u>-butylcyclohexanol as well as with cholesterol to occur with retention of configuration. Thus, only <u>trans</u>-4-<u>t</u>-butylcyclohexyl acetate was produced from reaction of <u>trans</u>-4-<u>t</u>-butylcyclohexanol with acetic acid using Ⓟ-$AlCl_3$ and cholesteryl acetate was the only observed product from the reaction of cholesterol with acetic acid catalyzed by Ⓟ-AlCl$_3$. Other products could not be detected either by gas-liquid chromatography or nuclear magnetic resonance experiments. This information suggests that the carbon oxygen bond in the alcohol is not broken during the esterification process and that the acid catalyst complexes with the carboxylic acid only. The transition state below seems likely from these experiments.



All substituted benzoic acids which were examined in competitive esterification rate studies reacted less rapidly than did benzoic acid itself under identical conditions. We believe this results from complexation between the substituent and the Ⓟ-AlCl$_3$ and are currently investigating substituted benzoic acids with substituent groups which are not able to complex. Relative esterification rates for substituted benzoic acids are also given in Table III.

Table III
Relative Rates - Substituted Benzoic Acids[a]

Substituent	Rates, k_x/k_H
H	1.00
p-Cl	0.57
m-Cl	0.65
p-Br	0.52
p-OEt	0.33

a. At 65° with 1-butanol, 20:1 excess over the total acids.

Greater reactivity was noted in reactions run in benzene solutions than in carbon disulfide. This effect is due to the swelling of the polymer in benzene which is greater than the comparable swelling possible in carbon disulfide as well as to the higher maximum temperature possible in the former solvent.

The polymer protected aluminum chloride was also shown to be an effective catalyst for transesterification. Treatment of n-butyl propionate with 1-hexanol and Ⓟ-$AlCl_3$ for 43 hours at 95° gave n-hexyl propionate in 57% yield. The non-catalyzed reaction under identical conditions produced only 8% yield of the n-hexyl ester.

Investigations are in progress concerning other applications of Ⓟ-$AlCl_3$ and its derivatives in synthetic transformations.

Acknowledgements: Support from the National Science Foundation (Grant No. GP 33566) and the Research Corporation is gratefully acknowledged. In addition, we thank the National Institute of Health-General Medical Sciences for a special post-doctoral fellowship for one of us (ECB).

REFERENCES

1. On leave (1972-1973) from Rollins College, Winter Park, Florida.

2. Fellow of the Alfred P. Sloan Foundation, 1971-73; to whom correspondance concerning this work should be addressed.

3. D.C. Neckers, D.A. Kooistra, and G.W. Green, J. Am. Chem. Soc., 94, 9284 (1972).

4. Not all ways in which polymer protected reagents can be used are advantageous For example, throughout the literature, various workers have used Friedel Crafts reactions on polymer supports. Recent examples were reported by Hayatsu and Khorana, J.Am.Chem.Soc., 88, 3182 (1966); ibid., 94, 4855 (1972). In the latter case, an asymmetric synthesis on a polymer support was reported. We urge precaution in the use of $AlCl_3$ in polystyrene reactions. The bound complexes which it forms with polystyrene-divinylbenzene copolymer beads are very hard to destroy so that $AlCl_3$ surely remains after typical and even not so typical wash procedures. The presence of $AlCl_3$ can be detected by the new band at 1650 cm^{-1}. If $AlCl_3$ is held on the polymer it may be partially released, perhaps not advantageously, later in the reaction sequence.

5. The water soluble complex is formed[3] from styrene-divinylbenzene (1.8%) copolymer beads (100-200 mesh). It contains 0.57% Al.

6. Products were identified by comparison of spectral characteristics with those of known samples.