2,6-DICHLOROPYRIDINE-2,6-^{14}C

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SUMMARY

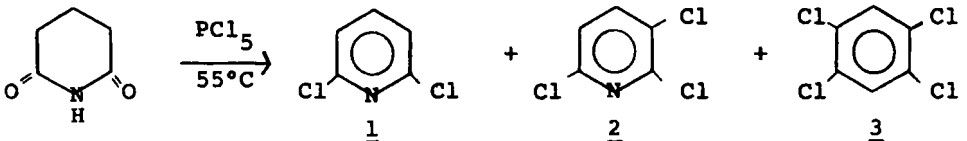
2,6-Dichloropyridine-2,6-^{14}C with a specific activity of 18.79 mCi/mmole was prepared in a 78% yield *via* the reaction of glutarimide-2,6-^{14}C and PCl_5. This represents a marked improvement over previously reported yields *via* this process.

Key Words: 2,6-Dichloropyridine-2,6-^{14}C, Glutarimide-2,6-^{14}C, Chlorination

INTRODUCTION

Snythetic efforts in this laboratory periodically require the preparation of labeled 2,6-dichloropyridine as an intermediate in the preparation of radioactive tracers. A convenient route to the chloro-pyridines involves the treatment of glutarimide-2,6-^{14}C with phosphorous pentachloride(1,2). However, this reaction (Scheme 1) affords mixture of chlorinated pyridines with the desired 2,6-dichloro adduct representing only *ca* 35-40% of the mixture.

SCHEME 1



1 1.0: 2 1.4: 3 0.3

Furthermore, only 50 to 80% conversions are achieved thereby affording the desired product in only 20-30% yields. Therefore, a study of this reaction was undertaken to optimize the production of the 2,6-dichloro isomer with an attendant increase in yield. The results are reported below.

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DISCUSSION

The highest yield of 2,6-dichloropyridine is obtained by causing glutarimide to react with three equivalents of phosphorous pentachloride at ca 22°C over a 70-80 hr period using phosphorous trichloride as the solvent.

Using glutarimide prepared from glutaronitrile(1) under these conditions isolated yields of 74% and 9% respectively were obtained for 2,6-dichloropyridine(1) and 2,3,6-trichloropyridine(2). Calculated yields of 79% and 9% respectively based upon the glc area percentages of 1 and 2 in the chlorinated product prior to separation agree well with the above results. Owing to this close correlation, the results of subsequent studies listed in Table I were based upon the glc analyses of the isolated chlorinated mixture.

When the above reaction was repeated using glutarimide purchased from Eastman Chemicals (Table I, Reaction B) the yields of 1 and 2 increased to 90% and 9% respectively affording a 99% overall yield of chlorinated products. However, the relative ratio of 1 to 2 remained constant.

Decreasing the reaction time from 72 hr to 22 hr (Reaction C, Table I) again affords a 9.0:1.0 glc area ratio of 1:2. However, the respective yields have decreased owing to incomplete reaction. The reaction is believed to be complete after ca 50 hr at which time a clear solution results when Eastman glutarimide is used. Likewise as is demonstrated in Reaction D, the use of less than three

equivalents of PCl_5 results in lower product yields again due to incomplete reaction.

Finally, the effects of temperature upon the reaction were briefly investigated. A PCl_3 solution of crude glutarimide was heated to 70°C and 3 equivalents of PCl_5 added. The mixture was heated at 75-80°C for 0.5 hr and subsequently at 100°C for 1 hr. The product distribution listed in Table I (Reaction E) was obtained. The higher temperatures favor formation of 2 as expected from the work of Meikle and Williams(2). The low overall yield is due in part to the presence of an insufficient quantity of PCl_5 since the formation of 2 and 3 would presumably require four and five equivalents of PCl_5 respectively.

The conditions of Reaction A were subsequently used to prepare 2,6-dichloropyridine-2,6-^{14}C in a 78.3% yield (Table I, Reaction F) which is a considerable improvement over the 20% yields previously encountered.

CONCLUSION

High yields of 2,6-dichloropyridine can readily be obtained from the reaction of glutarimide and PCl_5 at ca 22°C using PCl_3 as the solvent. Furthermore, it appears feasible that by adjusting the mole ratio of PCl_5 and the reaction temperature, one can selectively control the reaction to favor the chlorinated pyridine of choice.

EXPERIMENTAL

Chemicals

The glutarimide used in Reactions B, C, and D was purchased from Eastman Chemicals, whereas that in A, E, and F was prepared from potassium cyanide (Fisher) and 1,3-dibromopropane (Aldrich) in a two step process(1). The potassium cyanide-^{14}C (specific activity = 9.99 mCi/mmole) was purchased from Pathfinder.

Gas Chromatography

Glc analyses for Reactions A-E were performed on a Hewlett-Packard 5830A instrument using a 2' x 1/4" s.s. column containing 10% SE 30 on Chromasorb WHP. The following conditions were used:

temp 1 = 50°C	temp 2 = 250°C
time 1 = 0.5 min	time 2 = 2.0 min
rate = 20°C/min	He Flow = 50 ml/min

Under these conditions, authentic samples of 2,6-dichloropyridine 1, 2,3,6-trichloropyridine 2 and 2,3,5,6-tetrachloropyridine 3 possessed retention times of 3.2 min, 4.3 min, and 5.1 min respectively.

The radioactive sample was analyzed on a Barber Coleman Model 5000 instrument using a 4' x 1/8" glass column containing 5% DC-410 on Gas Chrom Q. The sample was analyzed isothermally at 110°C with a helium flow of 50 ml/min (Rt 1 = 2.2 min, Rt 2 = 4.5 min).

TABLE I

Reaction #	Weight (g) Glutarimide	Weight (g) Chlorinated Products	Glc Area Percent[1] 1	2	3	Percent Yield[2] 1	2	3
A	0.9181	1.0811	88	12	0	79	8.4	0
B	0.9933	1.3275	89	11	0	90	9.0	0
C	0.9944	0.8626	90	10	0	60	5.2	0
D	0.9236	0.4911	84	16	0	34	5.2	0
E	1.0988	1.0593	33	62	3	24	37	1.6
F	0.4637	-				78.3[3]	7.6[3]	

1. Hewlett Packard 5830 A instrument used.
2. Based upon glc area percent, no internal standard used.
3. Percent yield of isolated product.

Radiometric Determination

The radioactivity was determined in a Packard Tri-Carb Liquid Scintillation Spectrometer using New England Nuclear Aquesol universal liquid scintillation cocktail. Triplicate assays were taken.

The radiochemical purity was determined by spotting a sample along with standard samples of 1 and 2 on a 2" x 8" Silica Gel 60-F254 plate and developing the plate with a 1:1 (v/v) solution of n-hexane-benzene. The plate was scanned on a Vanguard auto scanner, scraped into 5 mm sections and the sections placed in 50% aqueous methanol. The mixture was diluted with Handiflur liquid scintillation cocktail and counted. A Histogram analysis of the data affords 1 with a radiochemical purity of 99.9%

SYNTHESIS

Reaction A

To 918.1 mg (8.116 mmole) of glutarimide in a 100 ml round-bottomed flask equipped with a magnetic stirring bar and drying tube, was added 5 ml of PCl_3 and 5.38 g (25.8 mmole, 3.18 eq) of PCl_5. After 89 hr of stirring at ca 22°C, the hazy solution was cooled to -8°C, treated cautiously with ice and water (~25 ml total) and the resultant mixture stirred ca 0.5 hr. The mixture was extracted continuously

for 6 hr with 15 ml of n-pentane to afford upon solvent removal 1.0811 g of white crystalline residue. The product was dissolved in 3 ml of C_6H_6 and a sample analyzed by glc (Table I). The remaining solution was passed through 100 g of Silica Gel G-60 (70-230 mesh) with a 1:1 (v/v) solution of n-hexane-benzene to afford 135.0 mg of 2 (0.740 mmole), 855.8 mg 1 (5.782 mmole) and 46.6 mg of a mixture containing by glc analysis 80 area percent 1 and 20 area percent 2. The latter mixture was considered in determining the total yields of 1 and 2 in Table I.

Reaction B

Following the above procedure, 993.3 mg (8.878 mmole) of glutarimide was caused to react with 5.54 g (26.6 mmole, 3.0 eq) of PCl_5 in 5 ml of PCl_3. A clear solution results after 42 hr at ca 22°C. The reaction was terminated after 67 hours to afford 1.3275 g of chlorinated products as a white crystalline solid.

Reaction C

Causing 994.4 mg (8.791 mmole) of glutarimide to react with 5.55 g (26.6 mmole, 3.05 eq) of PCl_5 in 5 ml of PCl_3 over a 22 hr period at ca 22°C affords 862.6 mg of white crystalline product.

The above reaction was repeated. After 22 hr at ca 22°C, the mixture was heated to 100°C affording a clear solution which was immediately cooled to -8°C. Following this procedure, 974.5 mg (8.615 mmole) of glutarimide is converted to 1.2552 g of product containing by glc analysis 67 area percent 1 (66% yield), 32 area percent 2 (26% yield) and 1 area percent 3 (0.3% yield). Thus, a 92.3% yield of chlorinated pyridines is obtained.

Reaction D

Following the second procedure in Reaction C, 923.6 mg (8.165 mmole) of glutarimide was caused to react with 1.88 g (0.903 mmole, 1.09 eq) of PCl_5 at ca 22°C over a 22.5 hr period. The mixture was then heated to 100°C to ensure complete reaction, cooled, and the product isolated in the usual manner to afford the results in Table I.

Reaction E

To 1.0988 g (0.971 mmole) of glutarimide, was added 5 ml of PCl_3 and the resultant mixture heated to 70°C. Phosphorous pentachloride, 6 g (0.029 mmole, 2.99 eq) was added and the mixture heated at 75-80°C for 0.5 hr and finally at 100°c for 1 hr. The solution color changed from yellow to red during the latter period. The usual isolation procedure affords 1.0593 g of light yellow crystalline product.

Reaction F. 2,6-Dichloropyridine-2,6-^{14}C

To 462.7 mg (4.099 mmole) of glutarimide-2,6-^{14}C in a 50 ml round-bottomed flask equipped with a stirring bar, was added, under a nitrogen atmosphere, 7 ml of PCl_3 and 2.82 g (13.5 mmole) of PCl_5. The mixture was stirred 72 hr resulting in a hazy solution. The solution was cooled to -8°C and treated cautiously with ice water. The chlorinated pyridines were isolated via continuous extraction and purified via column chromatography to afford 56.7 mg (0.311 mmole, 7.59% yield) of 2,3,6-trichloropyridine-2,6-^{14}C (Specific activity = 18.79 mCi/mmole) and 475.1 mg (3.210 mmole, 78.3% yield) of 2,6-dichloropyridine-2,6-^{14}C (Specific activity = 18.79 mCi/mmole). Both products were pure by glc analysis and the latter was determined to be 99.9% radiochemically pure by Histogram analysis.

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