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OXIDATIVE CHLORINATION OF [U-^{14}C] PHENOL

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SUMMARY

The preparation of [U-^{14}C] 2,4-dichlorophenol was formerly achieved by a Sandmeyer reaction with [U-^{14}C] 2,4-dichloroaniline but this sensitive step gave unreproductive yields in our hands.

We describe another route to [U-^{14}C] 2,4-dichlorophenol by the oxidative chlorination of [U-^{14}C] phenol. This shorter route is safer and gives satisfactory yields. The nature of the oxidizer is discussed.

Keywords : [U-^{14}C] phenol, [U-^{14}C] 2,4-dichlorophenol, chlorination.

RESULTS

2,4-Dichlorophenol is an intermediate widely used in organic synthesis. It has been prepared by many methods extensively described since the middle of 19th. Surprisingly no synthesis of carbon-14 labelled dichlorophenol could be found in the literature.

Chlorination of [ring U-^{14}C] acetanilide can be achieved by N-chloro succinimide to give [ring U-^{14}C] 2,4-dichloroacetanilide (1). Sandrock et al. used 3.3 equivalents of N-chlorosuccinimide to obtain [U-^{14}C] 2,4-dichloroaniline. The same stoechiometry of 3.3 was used to chlorinate [U-^{14}C] phenol but these authors obtained [U-^{14}C] 2,4,6-trichlorophenol. They also prepared [U-^{14}C] 2,4,6-trichlorophenol via the diazotization of [U-^{14}C] 2,4,6-trichloroaniline but this step gave a maximum yield of 5% (1).

We prepared [U-^{14}C] 2,4-dichlorophenol several times in our laboratories for custom syntheses of pesticides. We proceeded by chlorination of [ring U-^{14}C] acetanilide by molecular chlorine followed by substitution of the amino group by an hydroxyl function by a Sandmeyer reaction (scheme 1) (2). The work-up of this last step is critical and gave erratic yields: often about 50% but we obtained once 85% and once 8% with formation of [U-^{14}C] 1,3-dichlorobenzene as the main by-product.

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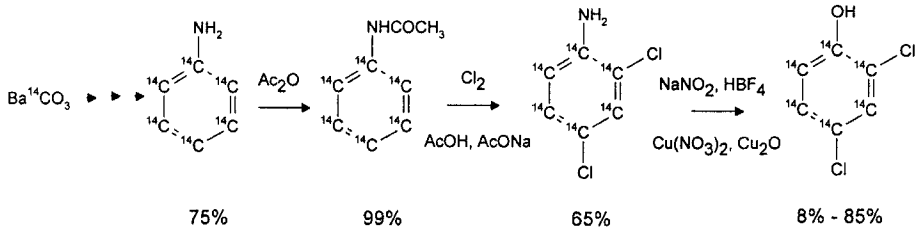
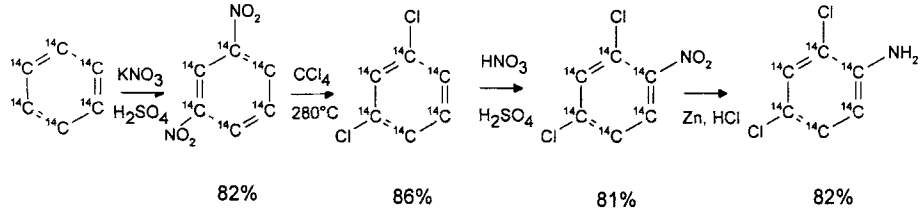


scheme 1 : chlorination of [ring U-^{14}C] acetanilide

The synthesis of [U-^{14}C] 2,4-dichloroaniline according to sheme 2 was described by Moriya (3). The following steps were: dinitration of [U-^{14}C] benzene into [U-^{14}C] 1,3-dinitrobenzene, substitution of the nitro groups by chlorine, nitration of [U-^{14}C] 1,3-dichlorobenzene and reduction of the nitro group into [U-^{14}C] 2,4-dichloroaniline.

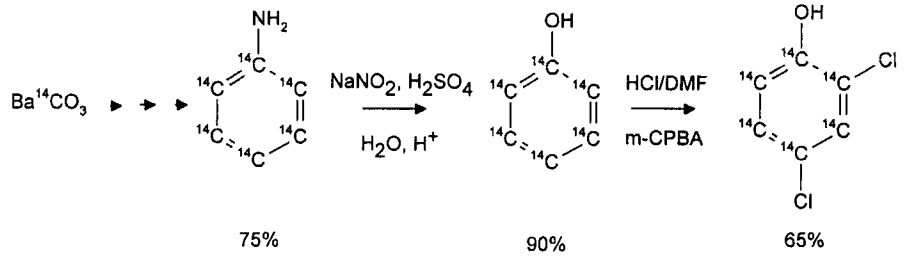


scheme 2 : preparation of [U-^{14}C] 2,4-dichloroaniline

This preparation was attempted in our laboratories. The chlorination which takes place in a sealed tube at high temperature gave hazardous explosion in the steel bomb and radioactive contamination occured (2).

From our own experience and from some literature reports, it seemed that the Sandmeyer reaction on [U-^{14}C] chlorinated anilines was the critical step of the preparation of [U-^{14}C] chlorinated phenols.We felt that this step should be circumvented.

Recently, we were interested by a new preparation of [U-^{14}C] 2,4-dichlorophenol involving the direct chlorination of [U-^{14}C] phenol. We used the method described by Chung and co-workers (4), which consists in the oxidative chlorination of phenols with hydrogen chloride/m-chloro perbenzoic acid (m-CPBA)/N-N-dimethyl formamide system, and we found that it can be easily applied to our labelled preparation (scheme 3).



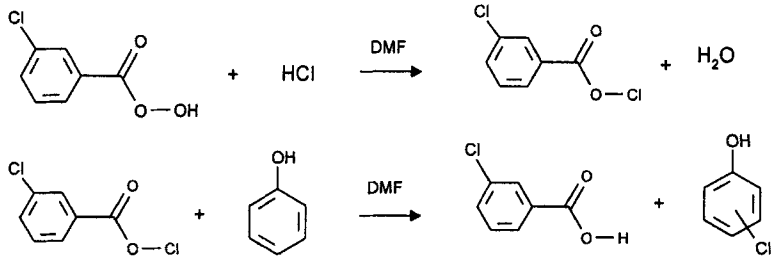
scheme 3 : chlorination of [U-^{14}C] phenol

[U-^{14}C] Benzene was prepared by the classical procedure (5). [U-^{14}C] Aniline was prepared by mono nitration of [U-^{14}C] benzene and reduction of the nitro group by sodium hypophosphite with palladium on charcoal (6). This reduction of [U-^{14}C] nitrobenzene into [U-^{14}C] aniline can also be achieved by many other reagents (7 to 10).

DISCUSSION

Reaction of peracid with halide salts has been described for about thirty years (11). The chlorine ion is oxidized in a positive chlorine and form an acyl hypochloride. A recent review describes the use of electrophilic peroxides in functionalisation of aromatic rings (12). M. Yoshida and co-workers (13) used the nitrobenzene sulfonyl peroxyde (NBSP) to achieve the chlorination of anisole. NBSP is assumed by these authors to be a better reactant than m-CPBA because nitrobenzene sulfonate is very stable and acts as a very good leaving group. M. Yoshida and co-workers used acetonitrile as solvent and triethylamine hydrochloride as source of chlorine. In fact, they did not obtain the halogenation of anisole with m-CPBA under these conditions. Anisole was chlorinated by NBSP with a 76% yield (determined by GC).

Chung and co-workers, unfortunately not cited in the review of Yoshida (12), used a hydrogen chloride/m-CPBA/N-N-dimethyl formamide (DMF) system. Under these conditions, chlorination of anisole was obtained with a 99% yield (90.8% for 4-chloro anisole with formation of 9.2% of 2-chloro anisole - determined by GC) (4). Chung and co-workers described chlorination of phenol to mono-, di-, or trichlorophenol depending on stoechiometry of HCl/m-CPBA versus phenol (4). They also described chlorination of various aromatics such as cresols, nitrophenols, naphtols, guaiacol and many substituted acetanilides with generally high yields and a good regioselectivity (4,14). Probably the dimethylformamide, acting as an aprotic dipolar solvent, aids the stabilisation of the positive chlorine. The mecanism can be written as follows :



The formed 3-chloro benzoic acid can be removed from the reaction mixture by extraction with potassium bicarbonate.

The reaction, which takes place at room temperature for twenty minutes, must be monitored by GC because no separation of mono-, di-, and tri-chlorophenols can be easily obtained by TLC monitoring.

Under the conditions described by Chung (4), [U-^{14}C] 2,4-dichlorophenol was obtained from [U-^{14}C] phenol with a 61% yield after purification. For this preparation, we used [U-^{14}C] sodium phenate. The stoechiometry of HCl was 3.5 (1 equivalent to liberate the phenol and 2.5 equivalents for the chlorination). The stoechiometry of m-CPBA was 2.2 equivalents.

One year later we needed another preparation of [U-^{14}C] 2,4-dichlorophenol. The m-CPBA used was contaminated by m-chlorobenzoic acid and we isolated large quantities of [U-^{14}C] 4-chlorophenol.

In a further preparation we chlorinated this [U-^{14}C] 4-chlorophenol in [U-^{14}C] 2,4-dichlorophenol. For this latter preparation, we were interested to form about 90% of [U-^{14}C] 2,4-dichlorophenol (expected for the synthesis of a pesticide) and 10% of [U-^{14}C] 2,4,6-trichlorophenol (expected for a study on its chemical degradation), so we added a slight excess of HCl/m-CPBA to obtain the mixture ([U-^{14}C] 2,4-dichlorophenol: 84% - [U-^{14}C] 2,4,6-trichlorophenol: 12% - determined by GC) in one experiment

EXPERIMENTAL

Materials and methods :

Thin layer chromatography (TLC) was performed on 60F 254 silicagel.

Radioactive TLC were recorded on a Berthold system, model LB 511.

Gas chromatography analyses were carried on a Varian 3300 unit with FID detector and proportional gas counter for radioactive detection after reduction in [^{14}C] methane on platinium at 750°C (Raga from Raytest). The column was a DB-17 megabore (30 m) operating with a temperature gradient from 100°C to 170°C. [^{14}C] labelled products were identified by co-injection with authentic samples.

Mass spectra were obtained from a Finnigan Mat 4600 quadrupol apparatus.

m-Chloroperbenzoic acid was purchased from Janssen Chimica. This commercial product contains amounts of 3-6% of m-chlorobenzoic acid and 19-22% of water. m-CPBA, in solution in chloroform was dried twice on sodium sulfate and evaporated to dryness, protected from light and handeled under nitrogen, until constant weight. The purity was estimated to be 85%.

N-N-Dimethylformamide was distilled over calcium hydride before use.

[U-^{14}C] phenol : A solution of sulfuric acid (4.6 mL of concentrated sulfuric acid in 30.3 mL of distilled water) was added to [U-^{14}C] aniline (18.25 mmol - 1090 mCi). The reaction vessel was equiped with a condenser and flushed with nitrogen. The reaction mixture was stirred untill solubilisation occured. A cooling bath was added and sodium nitrite (1.328 g, 19.24 mmol) was added gradually for fifteen minutes. The cooling bath was removed and the diazonium salt was heated to 50°C for two hours with evolution of nitrogen. After cooling at room temperature, diethyl oxyde (100 mL) was added and [U-^{14}C] phenol was extracted with three volumes of additionnal diethyl oxyde (100, 50 and 50 mL). The combined ethereal extracts were washed with a saturated solution of sodium hydrogenocarbonate and water. Then [U-^{14}C] phenol was extracted by a 0.1N solution of sodium hydroxyde (16.5 mmol - 990 mCi - yield 90%). Mass spectra (DCI/NH4) showed the labelled molecular peaks (peak 100%: 95 - p+1, peak 85%: 97 - p+3, peak 65%: 99 -p+5 etc...). Purity (99%) was checked by TLC on silicagel (toluene:80 ethylacetate:20). Specific activity : 62 mCi/mmol.

[U-^{14}C] 2,4-Dichlorophenol from [U-^{14}C] phenol : [U-^{14}C] sodium phenate (7 mmol - 360 mCi) was dried under vacuum. A 3.4 N solution of gaseous hydrogen chloride in dimethylformamide (7.2 mL - 24.5 mmol) and dimethylformamide (10 mL) were added. m-CPBA (3.13 g - purity 85% - 15.4 mmol) was added in one portion. The reaction mixture was vigorously stirred at room temperature for twenty minutes. TLC monitoring showed no residual [U-^{14}C] phenol. DMF was removed by vacuum distillation and [U-^{14}C] 2,4-dichlorophenol (4.3 mmol - 220 mCi - yield : 61%) was isolated by column chromatography

on silicagel using hexane/methylene chloride (70/30) as eluent. Purity (98%) was checked by TLC on silicagel (hexane:70 methylene chloride:30). Mass spectra (EI) showed the labelled molecular peaks (main molecular peak : 164 - p+2). Specific activity : 51.4 mCi/mmol.

[U-^{14}C] 2,4-Dichlorophenol from [U-^{14}C] 4-chlorophenol : A 4.8 N solution of hydrogen chloride in dimethylformamide (2 mL - 9.6 mmol) and dimethylformamide (10 mL) were added to [U-^{14}C] 4-chlorophenol (6.5 mmol - 390 mCi). m-CPBA (1.5 g - purity 85% - 7.4 mmol) was added in one portion. After twenty minutes stirring at room temperature, GC analysis showed 65% of [U-^{14}C] 2,4-dichlorophenol and 35% of [U-^{14}C] 4-chlorophenol. Additionnal m-CPBA (0.55g - 2.7 mmol) was added. After twenty minutes of additionnal stirring, GC analysis showed 80% of [U-^{14}C] 2,4-dichlorophenol and 20% of [U-^{14}C] 4-chlorophenol. m-CPBA (0.1 g - 0.49 mmol) was added and the reaction mixture was stirred overnight. 84% of [U-^{14}C] 2,4-dichlorophenol, 1.5% of [U-^{14}C] 4-chlorophenol and 12% of [U-^{14}C] 2,4,6-trichlorophenol were obtained. Methylene chloride was added and 3-chlorobenzoic acid was extracted by a potassium bicarbonate solution. Solvents were removed by vacuum distillation and the products were separated by column chromatography on silicagel eluted by hexane-ethylacetate (90/10). [U-^{14}C] 2,4-dichlorophenol (250 mCi) was obtained with a 64% yield (purity checked by GC : 99% - mass spectra (EI) m/z : 164 - p+2). [U-^{14}C] 2,4,6-trichlorophenol (30 mCi) was obtained as a by-product with a 7.7% yield (GC purity : 98% - mass spectra (EI): main molecular peak : 198 -p+2 - specific activity : 62 mCi/mmol).

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