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# NEW PROCESSES FOR THE SYNTHESIS OF 2,6-DICHLORO-3-METHYLANILINE-Ph-UL-$^{14}$C AND METHYL 6-CHLOROANTHRANILATE-Ph-UL-$^{14}$C

L. H. McKendry and M. A. Stanga*
DowElanco
9330 Zionsville Road
Indianapolis, Indiana 46268

*Dow Corning
2200 W. Salzburg Road
Auburn, Michigan 48611

## SUMMARY

Two new processes were developed for the synthesis of 2,6-dichloro-3-methylaniline-Ph-UL-$^{14}$C (1), a key intermediate in the synthesis of a DowElanco experimental product presently being considered for commercialization. Both processes afford product in much higher yields than that previously reported in the literature. One of the processes was subsequently applied to the synthesis of methyl 6-chloroanthranilate-Ph-UL-$^{14}$C (12), used as an intermediate for a second potential product.

**Key Words:** Carbon-14, 2,6-dichloro-3-methylaniline, methyl 6-chloroanthranilate, chlorination.

## INTRODUCTION

2,6-Dichloro-3-methylaniline (1) and methyl 3-chloroanthranilate (12) are key intermediates in the synthesis of two experimental compounds presently being considered for commercialization as agricultural products by DowElanco. The radiolabeled samples of 1 and 12 were required to appropriately label the end products for the environmental and metabolism studies required for their registration. The initial request required the synthesis of 1. At the time this research was conducted, the only published process (1,2) afforded unlabeled 1 in <20% yields (3). A vastly improved procedure was required for the radiolabeled sample.

## DISCUSSION

Starting with the readily available precursor m-toluidine, two new processes were developed which afford 2,6-dichloro-3-methylaniline in good yield. The first process is depicted in Scheme I and represents that which was used for the tracer synthesis.

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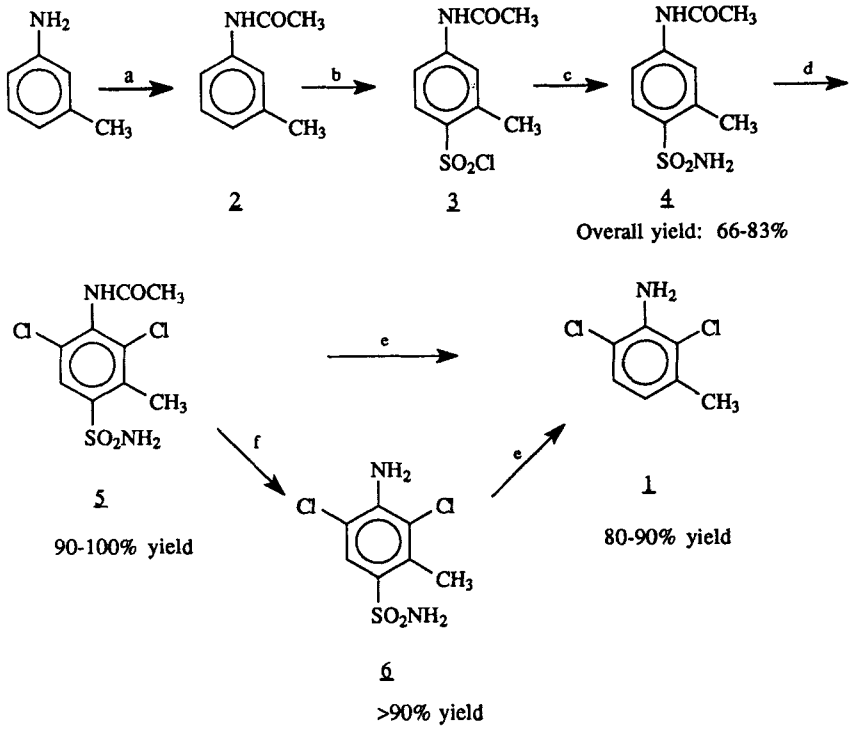
**Scheme I[a]**




[a]Key (a) $(MeCO)_2O$, $Et_3N$, $Et_2O$ or $CH_2Cl_2$ (b) $ClSO_3H$ (c) $CH_2Cl_2$, conc. $NH_4OH$ (d) $Cl_2$, NaOAc, $CF_3CO_2H$ or HOAc (e) $H_2SO_4$ (f) 1N NaOH

Preparation of acetanilide 2 (Step a) affords product in 70-100% yields. Steps b and c are similar to those reported by O. G. Backeberg (1). However, the process was modified by using methylene chloride during the isolation of sulfonyl chloride 3 and in its subsequent conversion to sulfonamide 4 which resulted in a yield enhancement from 48% to yields ranging from 66% to 83%.

The chlorination of anilide 4 (Step d) has not been previously reported. The chlorination is best accomplished in trifluoroacetic acid in the presence of 2 equivalents of sodium acetate (or sodium trifluoroacetate). The salt may be acting as more than an HCl sink since a significant rate enhancement was observed even in the milligram scale reactions. The process afforded 90-100% yields of product in the pilot runs and a 71% yield in the tracer synthesis.

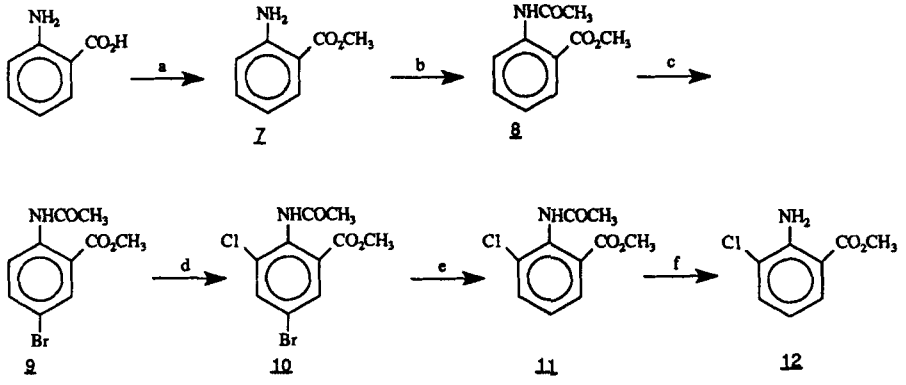
Anilide 5 can be converted directly to 2,6-dichloro-3-methylaniline in >90% yields via acid hydrolysis as depicted in Step e, but the product is contaminated with ca. 1% 3-methyl-2,4,6-trichloroaniline

which is very difficult to separate on a milligram scale. Therefore, the alternate 2-step approach was devised. The intermediate sulfonamide 6 can readily be separated from non-acidic impurities such as 3-methyl-2,4,6-trichloroaniline via extraction of the basic solution. Subsequent acidification affords intermediate 6 in >91% yield which can then be hydrolyzed to 1 in an 87% yield.

The process depicted in Scheme I was subsequently used to prepare 41.9 mCi of 97.3% radiochemically pure 1-Ph-UL-$^{14}$C with a specific activity of 22.4 mCi/mmole. The above process should have general applicability for the synthesis of *ortho*-chloroanilines providing the other ring substituents are stable to the chlorosulfonation conditions.

A second method was also developed for the synthesis of 1 which involved selective bromination in the 4-position of anilide 2 followed by chlorination and subsequent debromination. Although this process was not used for the synthesis of radiolabeled 1, it has since been modified and represents a commercially viable process with general applicability (4). Its versitility was demonstrated in the synthesis of a radiolabeled sample of methyl 3-chloroanthranilate (Scheme II) which was required as an intermediate for a second DowElanco experimental product.

**Scheme II[a]**




[a]Key (a) $Et_2O$, $CH_2N_2$ (b) $CH_2Cl_2$, $Et_3N$, $(CH_3CO)_2O$ (c) $Br_2$, HOAc (d) $Cl_2$, $CF_3CO_2H$, NaOAc (e) EtOH, 10% Pd/C, $H_2$ (f) MeOH, $H_2SO_4$

The 6-step process afforded 75.9 mCi (63.5% yield) of >98% radiochemically pure methyl 3-chloroanthranilate-Ph-UL-$^{14}$C as a white solid.

## EXPERIMENTAL

The GLC analyses were obtained either using a Hewlett Packard 5830A instrument equipped with (A) a 2' x 4 mm glass column packed with 10% OV17 on 80/100 Chromosorb WHP and (B) a 15 m x 0.35 mm x 1.5 m J&W DB-1 column (Temp 1=100°C, Time 1=2 min, Rate=20°C, Temp 2=250°C, Time 2=10 min, $N_2$ Flow=60 ml/min), or a Hewlett Packard 5890A instrument equipped with a J&W 15 m x 0.32 mm x 0.25 mm DB-5 column under either of the following conditions: (C) Temp 1 = 100°C, Time 1 = 2 min, Rate = 20°C/min, Temp 2 = 280°C, Time 2 = 5 min at 2 ml/min He flow; (D) Temp 1 = 60°C, remaining conditions as for (C). The GC/MS spectra were obtained in a Hewlett Packard 5890A instrument equipped with a HP 5971 MSD and containing a J&W 15 m x 0.26 mm x 0.25 m DB-5 column (Temp 1=100°C, Time 1=2 min, Rate=20°C, Temp 2=280°C, Time 2=5 min, He Flow=1.25 ml/min, 50:1 split injection, EI(+ ion) mode, 70 eV). The results are given as area%. No internal standards were used. The mass spectral analyses were performed in a Finnigan 4615 instrument (EI mode, 70 eV, 1100 V electron multiplier) using either direct probe or GC/MS (10 m x 0.25 mm x 0.25 m DB-1, Temp 1=100°C, Time 1=0.1 min, Rate=20°C/min, Temp 2=220°C, Time 2=5 min. The thin layer chromatographic (TLC) analyses were performed on Whatman 5 x 20 cm KC18F reverse phase plates and on either EM Laboratories 5 x 20 cm Kieselgel silica gel 60 F254 plates or Analtech 5 x 20 cm silica gel GF plates. The plates containing tracer were radioscanned using a Radiomatics RSTLC radioscanner. The reverse phase HPLC analyses were conducted using a Water's 600E system controller, U6K injector, and a Novapak C18 column (8 x 10 RCM) connected in series with a Water's 990 photodiode array UV detector and a Beckman 171 radioactivity detector under either of the following set of conditions: (A) 100% $H_2O$-100% $CH_3CN$, linear gradient, 2 ml/min, 25 min; 100% $CH_3CN$, 2 ml/min, 5 min; UV 254 nm. (B) 25:75 $CH_3CN$:$H_2O$, 1 ml/min, 40 min; 25-100% $CH_3CN$, linear gradient, 1 ml/min, 10 min; 100% $CH_3CN$, 2 ml/min, 10 min.

### 3'-Methylacetanilide-Ph-UL-$^{14}$C (2-$^{14}$C).

A 220.2 mCi (8.405 mmole) sample of *m*-toluidine-Ph-UL-$^{14}$C (NEN, Lot#2406-269, 98.5% radiochemically pure, 26.2 mCi/mmole) was caused to react with 1.0 ml (10.6 mmole) of acetic anhydride in the presence of 1.4 ml (10.0 mmole) of $Et_3N$ and 15 ml of $Et_2O$ at reflux over a 4 hr period. Subsequent isolation afforded 1.261 g (8.449 mmole, 100% yield) of 2-$^{14}$C as a yellow oil which was used for subsequent reactions prior to crystallization; GLC (Condition A) 5.55 min (99.3%, Rt standard 5.49 min); GLC (Condition B) 4.75 min (98.0%, Rt standard 4.75 min), TLC radioscan (5 x 20 cm EM plate, 1:1 (v/v) n-hexane:EtOAc, $R_f$ 0.217 (100%).

**4'-Aminosulfonyl-3'-methylacetanilide-Ph-UL-$^{14}$C (4)**

A 625.2 mg (4.190 mmole) sample of 2-$^{14}$C was transferred to a pear-shaped flask and cooled in an ice bath. Chlorosulfonic acid, 2 ml, was added and the stirred solution heated at 60°C under a $N_2$ atmosphere for 2 hr. The solution was cooled in an ice bath and added dropwise to a mixture consisting of 20 g of ice, 2 ml of $H_2O$, and 10 ml of $CH_2Cl_2$. The reaction flask was rinsed $CH_2Cl_2$ and $H_2O$. The phases were mixed, separated, and the $CH_2Cl_2$ phase dried ($MgSO_4/NaSO_4$) and filtered. The filtrate containing sulfonyl chloride 3-$^{14}$C was stirred and cooled in an ice bath and 5 ml of conc. $NH_4OH$ added dropwise. The resultant mixture was stirred at room temperature for 1.25 hr causing precipitation. The mixture was filtered and the precipitate washed with $H_2O$ and $Et_2O$. The preciptitate was dissolved in 10 ml of refluxing MeOH and filtered into a tared flask. The reaction flask and filter were rinsed with refluxing MeOH. The solvent was removed under a stream of $N_2$ and the residue dried at 50°C/0.5 mm for 1 hr to afford 639.0 mg (2.799 mmole, 66.8% yield) of 4-$^{14}$C as a white solid. Reverse phase HPLC 9.52 min (99.9% radiochemically pure); TLC (5 x 20 cm plate, 8:2 (v/v) EtOAc:hexane) $R_f$ 0.204 (99% radiochemically pure).

**4-Aminosulfonyl-2,6-dichloro-3-methylaniline-Ph-UL-$^{14}$C (6)**

Anilide 4 (639.0 mg, 2.799 mmole) was dissolved in 30 ml of $CF_3CO_2H$ and the stirred solution purged with $N_2$. Sodium acetate, 165.9 mg (2.023 mmole), and 297.9 mg of $FeCl_3$ (5) were added. The flask was equipped with a double balloon filled to a 15 cm diameter with $Cl_2$ (6). The flask was evacuated and filled with $Cl_2$ twice. The ice bath was removed and the solution stirred at room temperature for 17 hr. An additional 100 mg of $FeCl_3$ was added and the flask evacuated and filled with $Cl_2$ as described above. The solution was stirred for an additional 22 hr. The solvent was removed under a stream of $N_2$ and the residue treated with 10 ml of $H_2O$ and 1 g of $NaHSO_3$. The mixture was stirred for 0.5 hr and filtered. The precipitate was washed with 5 ml of 1 N HCl and 2 x 5 ml of $H_2O$ to afford acetanilide 5-$^{14}$C. The precipitate 5 was dissolved in 15 ml of 1N NaOH and the solution heated at reflux for 6 hr and then allowed to cool and stir overnight. The solution was extracted with $CH_2Cl_2$ (1 x 5 ml, 5 x 2 ml) and the combined extracts washed with $H_2O$ (2 x 2 ml). The aqueous washes were added to the aqueous solution and the solution acidified with 2 ml (34.9 mmole) of HOAc. The resultant mixture was filtered and the precipitate washed with $H_2O$. The precipitate was transferred to a tared flask using MeOH. The MeOH solution of 6-$^{14}$C was analyzed *via* TLC (5 x 20 cm $SiO_2$ plate, 8:2 (v/v) EtOAc:hexane, $R_f$ 0.59 (97.1% radiochemically pure) and direct probe MS (EI mode, M/e 254 and 256 ($M^+$, 2 Cl present). The solvent was removed *in vacuo*

and the residue dried at 24°C/0.5 mm for 1 hr to afford 509.8 mg (1.998 mmole, 71.4 % yield) of aniline 6 as a tan solid.

**2,6-Dichloro-3-methylaniline-Ph-UL-$^{14}$C (1-$^{14}$C)**

A stirred mixture consisting of 509.8 mg ( 1.998 mmole) of 6, 1.0 ml of $H_2O$, and 1.61 ml of conc. $H_2SO_4$ was heated at 190°C under a $N_2$ atmosphere for 3 hr. The orange solution was cooled in an ice bath and 15 ml of $CH_2Cl_2$ added. The stirred mixture was made basic via dropwise addition of 13 ml of 5 N NaOH and 20 ml of $H_2O$ added. The $CH_2Cl_2$ phase was filtered through $Na_2SO_4/MgSO_4$ into a tared flask. The aqueous phase was extracted with $CH_2Cl_2$ (5 x 2 ml) and each filtered into the flask. The solvent was removed from the filtrate in vacuo at 24°C/40 mm and the residue dried further at 24°C/25 mm for 20 min to afford 330.1 mg (1.875 mmole, 93.8% yield) of aniline 1-$^{14}$C as a yellow solid. GLC (Condition A) Rt 6.55 min (99.9%), Rt standard 6.55 min; GLC (Condition B) Rt 6.53 min (97.9%) Rt (standard) 6.57 min; HPLC (System 1) 19.78 min (UV), 19.967 min (radioscan, 97.33% radiochemically pure); HPLC standard 1 (UV) 19.39 min. The unlabeled product prepared in the pilot runs was further characterized via NMR analysis.

**Methyl Anthranilate-Ph-UL-$^{14}$C (7)**

Anthranilic acid-Ph-UL-$^{14}$C (NEN lot # 2486-050, 112 mCi, 28 mCi/mmol) was esterified with ethereal diazomethane and the product purified via silica gel chromatography (20 g, 230-400 mesh, 1:1 (v/v) $CH_2Cl_2$:hexane for elution) and isolated in 100 ml of solution; GLC (Condition D) 5.74 min (99+%); GC/MS (Temp 1=60°C) 6.67 min M/e 151 ($M^+$), 119 ($M^+$-32), 92 ($M^+$-$CO_2CH_3$). The solvent was removed in vacuo and the product used immediately in the second step of the sequence.

**Methyl N-Acetylanthranilate-Ph-UL-$^{14}$C (8)**

Radiolabeled 7 in 15 ml of $CH_2Cl_2$ was acetylated with acetic anhydride in the presence of triethylamine. The crude product was purified by column chromatography (21 g silica gel, 230-400 mesh, 1:1 (v/v) $CH_2Cl_2$:hexane (150 ml) followed by $CH_2Cl_2$) to afford 674 mg (3.49 mmol, 87% yield) of 8 as a white solid; GLC (condition C) 5.82 min (100%).

**Methyl 5-bromo-N-acetylanthranilate-Ph-UL-$^{14}$C (9).**

Bromination of ester 8 was accomplished with $Br_2$ in HOAc. The process afforded 951.3 mg (3.49 mmol, 100% yield) of 9 as a light tan solid; GLC (Condition C) 7.389 min (99%).

**Methyl 5-bromo-3-chloro-N-acetylanthranilate-Ph-UL-$^{14}$C (10).**

The round bottom flask containing 9 was equipped with a 3-way stopcock and 30 ml of trifluoroacetic acid and 0.72 g (8.78 mmol) of sodium acetate added. The solution was cooled in an ice bath, and evacuated and purged with $Cl_2$ twice. The solution was stirred under a $Cl_2$ atmosphere at room temperature for 26 hours. Water, 5 ml, and 0.5 g of sodium bisulfite were added and the solution stirred at room temperature for 10 minutes. The aqueous $CF_3CO_2H$ was removed under a stream of $N_2$. The residue was treated with 20 ml of ethyl acetate and washed with 2 x 10 ml of $H_2O$. The organic layer was filtered through $Na_2SO_4$ into a round bottom flask and the solvent was removed in vacuo. The product was purified via silica gel chromatography (40 g of silica gel, 100 ml $CH_2Cl_2$ followed by 200 ml 8:2 (v/v) $CH_2Cl_2$/EtOAc) affording 984 mg ( 3.211 mmole, 92 % yield) of ester 10 as a white solid. GLC (condition C) 8.09 min (93.9%).

**Methyl 3-Chloro-N-acetylanthranilate-Ph-UL-$^{14}$C (11)**

The 50 ml round bottom flask was purged with $N_2$(g) and 54 mg of 10 % Pd-C in 10 ml ethanol added. Ester 10 was dissolved in 15 ml of ethanol and added to the flask. The system was evacuated and purged with $H_2$(g) three times. The mixture was stirred under $H_2$(g) for 2 hours. Subsequent GLC analysis indicated incomplete reaction. Therefore, 40 mg of 10% Pd-C was added in 3 ml of ethanol and the mixture stirred at room temperature for an additional 2 hours. The mixture was filtered through a plug of celite/$Na_2SO_4$ into a round bottom flask. The reaction flask was rinsed with 4 x 3 ml ethyl acetate and each filtered into the round bottom flask. The solvent was removed in vacuo to afford 614.1 mg (81% yield) of 11 as an off-white solid. GLC (Condition D) 9.07 min (100%).

**Methyl 3-Chloroanthranilate-Ph-UL-$^{14}$C (12)**

A solution consisting of 614.1 mg of 11 in 50 ml of anhydrous MeOH was stirred under a $N_2$ atmosphere and 1 ml of conc. $H_2SO_4$ added. The stirred solution was refluxed 48 hours. Solvent was removed in vacuo until approximately 10 ml of solution remained. Methylene chloride, 35 ml, was added and the solution extracted with 4 x 10 ml of $H_2O$. The combined aqueous layers were extracted with 2 x 5 ml of $CH_2Cl_2$. The combined $CH_2Cl_2$ solution was filtered through $Na_2SO_4$/$MgSO_4$ into a tared round bottom flask. The solvent was removed in vacuo affording 469 mg (2.54 mmol) of 12 as a white solid. GLC (Condition D) 7.33 min (92%), GC/MS (7.433 min) M/e 185&187 ($M^+$), 153&155 ($M^+$-$CH_3OH$), 125 (153-CO), 90 (125-Cl); TLC (1:1 $CH_2Cl_2$:hexane) $R_f$ 0.53 (99+% radiochemically pure).

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4. McKendry, L. H. and Zettler, M. W. -U. S. Patent 5,068,392 (1991).
5. Subsequent studies have demonstrated that $FeCl_3$ serves no useful purpose in this reaction.
6. The first balloon is inserted into the second. The $Cl_2$ will cause the inner balloon to rapidly loose its elasticity. However, the outer balloon is uneffected and therefore maintains a positive $Cl_2$ pressure over the reaction.