PESTICIDES LABELLED WITH ^{14}C.; IV. SYNTHESIS OF DIURON AND LINURON IN VARIOUS POSITIONS

J. Volford, E. Koltai, F. Kling and A. Volford*
Institute of Isotopes Co. Ltd.
H-1525, Budapest, P.O.B. 851. Hungary
*Technical University of Budapest
H-1111, Szt. Gellért tér 4.

SUMMARY

Diuron and Linuron, two herbicides, with very similar structures were labelled in their aromatic ring with ^{14}C. The yields of the synthesis (starting from $Ba^{14}CO_3$) was 8.5% and 4.8%, respectively. Linuron was also labelled with ^{14}C in its urea group with 33% yield.
Key words: Diuron, Linuron, 3,4-dichloro[U-^{14}C]aniline, herbicides, ^{14}C, synthesis

INTRODUCTION

Diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea] is a herbicide, that inhibits photosynthesis and used for the general weed control on non-crop areas[1]. Linuron [3-(3,4-dichlorophenyl)-1-methoxy-1-methyl urea] has a very similar structure, it inhibit photoelectron transport, is used as pre-emergency herbicides in asparagus, beans, peas, cotton, maize etc[2]... Both were labelled in their aromatic ring, moreover Linuron was also labelled in its urea carbon atom.

RESULTS

The synthesis of ring labelled Diuron (1) and Linuron (2) as Scheme 1 shows, started from 3-chloro[U-^{14}C]aniline (3) (it was prepared from [U-^{14}C]benzene according to our previous article[3]), acylated to 4 with acetic anhydride, then it was chlorinated by N-chlorosuccinimide. This reaction gave several products: 2,3-, 2,5-, and 3,4-dichloro acetanilide, but the main product was 3,4-dichloro-[ring U-^{14}C]acetanilide (6), more than 70% of the raw

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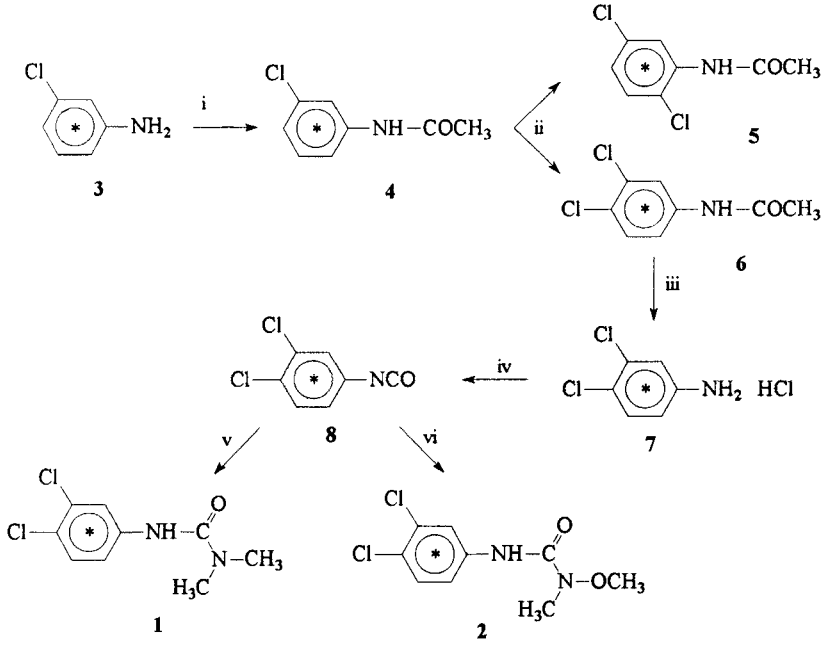
material. 6 was separated by chromatography; it was hydrolyzed with conc. HCl in ethanol to give 3,4-dichloro-[U-^{14}C]aniline (7). Then 7 was reacted with diphosgene (trichloromethyl chloroformate) to give the isocyanate 8, which reacted with dimethylamine and N,O-dimethyl hydroxylamine gave [ring U-^{14}C]Diuron (1) and [ring U-^{14}C]Linuron (2), respectively. The overall yields (calculated for $Ba^{14}CO_3$) were respectively 8.5 and 4.8%.

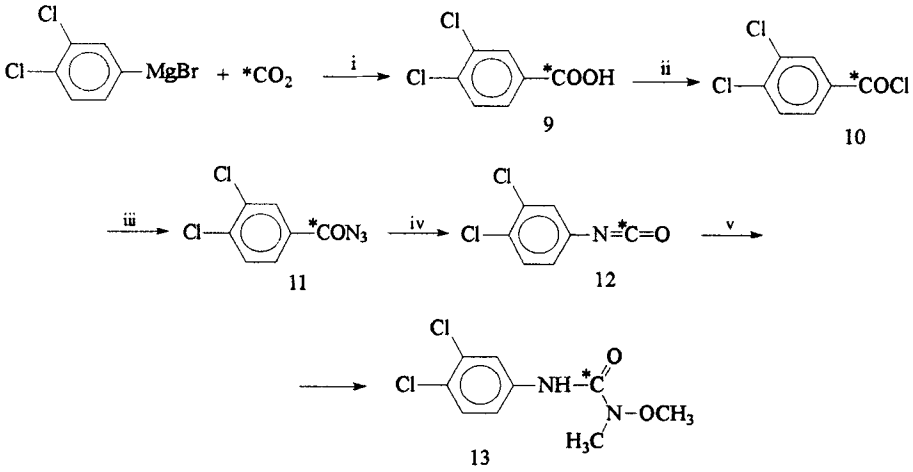
SCHEME 1.



i = acetic anhydride, acetic acid, room temp., overnight; ii = N-chlorosuccinimide, acetic acid, 2 days at room temp., then 2 h at 60°C; iii = conc. HCl, ethanol, 2 h reflux; iv = trichloromethyl chloroformate, benzene 2 h reflux; v = dimethylamine, dichloromethane, 2 h at room temp. vi = N, O-dimethyl hydroxylamine, dichloromethane, 2 h at room temp.

The synthesis of Diuron labelled in its urea carbon atom was published before[4]. But when we tried to apply this method for Linuron, the yield was very poor, probably because of the decomposition of the intermediate N-(trimethylsilylcarbonyl)-N,O-dimethylhydroxylamine, so another approach was needed as Scheme 2 shows. 3,4-Dichloro [7-^{14}C]benzoic acid (9) was prepared by the carbonation of 1,2-dichlorobromobenzene, it was transformed to its isocyanate (11), via a Curtius reaction[5], and finally 11 was reacted with N,O-dimethyl hydroxylamine to give [carbonyl-^{14}C]Linuron (12) with 33% overall yield.

SCHEME 2.



i = ether, r.t.; ii = $SOCl_2$,, reflux, 2 h; iii = NaN_3, acetone, 3 h, r.t.; iv = toluene, 80-100°C, 2 h; v = N,O-dimethyl hydroxylamine, dichloromethane, 2h, r. t.

EXPERIMENTAL

Melting points are uncorrected and were determined with a PHMK microscope. Chromatography was performed on Silica gel 60 HF_{254} plates (MERCK) and Silica gel 60 (0.063-1.00 mm), respectively. The spots were visualized by UV light and evaluated by a Berthold Tracemaster 20 scanner. HPLC was performed on a Gilson HPLC system on a Nucleosil 5C-18 column (acetonitrile - water 65:35; flow: 1.0 ml/ min). Radioactivity was measured on an LKB 1217 rack beta liquid scintillation counter. All the chemicals were purchased from Aldrich, except N,O-dimethyl hydroxylamine and 3,4-dichloro-bromobenzene, which were prepared according to known procedures[7,8]. Evaporations were performed in a rotavapor.

3-chloro[U-^{14}C]aniline (3)

It was prepared from Ba[^{14}C]O_3, as described earlier[3].

3-chloro[ringU-^{14}C]acetanilide (4)

3 (102 mg, 0.8 mmoles, 18.6 mCi) was dissolved in acetic acid (5 ml), then acetic anhydride (0.5 ml) was added and the mixture was kept overnight at room temperature. Then acetic acid was evaporated, the residue was treated with water (10 ml), and extracted with chloroform (3x7 ml). The extracts were washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. Chromatographically pure 4 was obtained with almost quantitative yield as a white solid (136 mg, 0.8 mmoles, 18.6 mCi). M.p.: 72-74°C (Lit.[9]: 78-79°C, or 72.5°C). TLC: benzene - ethyl acetate 1:1; Rf = 0.5)

3,4-Dichloro[ring U-^{14}C]acetanilide (6)

4 (136 mg, 0.8 mmoles, 18.6 mCi) was dissolved in acetic acid (1 ml) and 116 mg (0.87 mmoles) of N-chloro succinimide was added. The mixture was stirred for 72 hours at room temperature, and for 2 hours at 60°C. Then the mixture was worked up as 4. 142 mg

white solid was obtained, which - according to radio-TLC (benzene - ethyl acetate 1:1) - contained about 30% impurities (e. g. **5**). It was purified by chromatography (benzene - ethyl acetate 1:1) and 100 mg (0.49 mmoles, 11,4 mCi, 61%) of pure **6** was obtained (it contained - according to radio-TLC - less than 2% impurities). M. p.:116-119°C (Lit.[109]: 121°C).

3,4-Dichloro[U-^{14}C]aniline HCl (7)

6 (100 mg, 0.49 mmoles, 11.4 mCi) was dissolved in ethanol (10 ml), and conc. HCl (5 ml) was added. The mixture was refluxed for 2 hours, then the solvents were evaporated. The residue a colorless solid (102 mg, more than 100%), which was used for the next step without purification.

[ring U-^{14}C]Diuron (1)

7 (102 mg, 0.49 mmoles, 11.4 mCi) was suspended in benzene (5 ml), trichloromethyl chloroformate (diphosgene, 3 ml) was added, and the mixture was refluxed for 2 hours, then another portion of dipnosgene (1 ml) was added and refluxed for another hour. The solvents were evaporated and the residue was dissolved in dichloromethane (5 ml) and it was dropped into a solution of dimethylamine (33% in ethanol, 5 ml) at 0°C during 30 minutes. Then it was stirred for 1 hour at 0°C, then for another hour at room temperature. Evaporating the solvents the residue was 145 mg light brownish solid (>100%), which - according to radio-TLC - was **1** contained 3% impurities. It was purified by preparative TLC (benzene - ethyl acetate 1:1, 2 pieces of MERCK 60 PF_{254} plates, eluted with dichloromethane - ethanol 1:1). That way 87 mg of chromatographically (HPLC and radio-TLC) pure **1** was obtained (76%). M.p.: 151-154°C (Lit.[1]: 158-159°C). A_{sp}: 103 mCi/g; A_m: 24.1 mCi/mmol; A_t: 8.9 mCi.

[ring U-^{14}C]Linuron (2)

7 (1.20 g, 6.04 mmoles, 91.8 mCi)[11] was suspended in benzene (5 ml), 3 ml of diphosgene was added and the mixture was stirred and refluxed for 2 hours. Then another portion of diphosgene (2 ml) was added and it was refluxed for another hour. Then the solvents were evaporated, the residue was dissolved in dichloromethane (5 ml) and a solution of N,O-dimethyl hydroxylamine (1 ml, about 15 mmoles) in dichloromethane (3 ml) was added slowly (10 minutes). It was stirred for 1 hour at room temperature, then the solvent was evaporated. The residue (1.2 g of white solid) was purified by chromatography (benzene ethyl acetate 1:1), and the pure fractions were recrystallized from methanol (1 ml). 603 mg of **2** was obtained as white crystals. M.p.: 89-90°C (Lit.[2]: 93-95°C). It was pure by TLC and HPLC). A_{sp}: 65.24 mCi/g, A_m: 16,2 mCi/mmoles, A_t: 39.1 mCi.

3,4-Dichloro [7-^{14}C]benzoic acid (9)

A Grignard reagent was prepared from 3,4-dichlorobromobenzene (1.13 g, 5 mmoles), and magnesium turnings (168 mg, 7 mgA) in abs. ether (10 ml) on the usual way[6]. It was carbonated with 4 mmoles of $^{14}CO_2$ (generated from 792 mg of $Ba^{14}CO_3$, 50,45 mCi), decomposed with 2 N sulfuric acid (5 ml), extracted with ether, then the organic part was re-extracted with 2N NaOH (2x5 ml), and this extract was made acidic with cc. HCl (pH 1), and the precipitate was filtered and dried in exsiccator. 670 mg of **9** was obtained with 87% yield. A_{sp}: 43.90 mCi/mmol, A_t: 30.46 mCi. M.p.: 202-206°C (Lit[12].: 208-209°C).

3,4-Dichloro [7-^{14}C]benzoyl chloride (10)

9 was refluxed for 2 hours in thionyl chloride (10 ml), then the solvent was evaporated and the residue (750 mg colorless thick oil) was used without purification for the next step.

3,4-Dichloro [7-^{14}C]benzoyl azide (11)

10 was dissolved in dry acetone (4 ml) and this solution was dropped slowly (10-15 min) into a mixture of NaN_3 (700 mg, 10 mmoles) and acetone (2 ml). It was stirred for 3 hours, then icy water was added (20 ml), and the precipitated azide (**11**) was filtered, washed with water and dried in vacuum exsiccator. **11** was obtained as beige colored crystals (620 mg, 82%)

3,4-Dichlorophenyl-[^{14}C]isocyanate (12)

11 (2.9 mmoles) was dissolved in toluene (10 ml) and heated at 80°C while bubbled. Then it was heated at 100°C for 2 hours and the solvent was evaporated. **12** (560 mg, >100%) was obtained as brownish oil.

[carbonyl-^{14}C] Linuron (13)

12 (2.9 mmoles) was dissolved in dichloromethane (5 ml) and N,O-dimethyl hydroxylamine (0.6 ml) was added. The mixture was stirred overnight at r.t., then the solvent was evaporated and worked up as **2**. 497 mg (69%) of chromatographically pure **13** was obtained as white solid. A_{sp}: 34.01 mCi/g, A_m: 8.4 mCi/mmol, A_t: 16.71 mCi. M.p.: 90-91°C (Lit.[2]: 94-95°C).

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