Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXIX, No. 4.

THE RADIOLABELLED SYNTHESIS OF *N*-ETHYL-2-CHLORO-6-TRIMETHYLSILYLBENZAMIDE[Ring-^{14}C(U)], A FUNGICIDE CANDIDATE FOR WHEAT TAKE-ALL DISEASE

Brad D. Maxwell

Monsanto Company
700 Chesterfield Parkway North
St. Louis, Missouri 63198

SUMMARY

N-Ethyl-2-chloro-6-trimethylsilylbenzamide [Ring-14C(U)], **6**[1], was synthesized in five steps from [U-^{14}C]-benzoic acid **1** in an overall yield of 71%. Two key steps in the synthesis involve directed *ortho* metalation reactions[2] on the aromatic ring. Purification by Silica gel Flash Column Chromatography produced **6** with a radiochemical purity of 99%.

Key words: benzamide, directed *ortho* metalation reaction, fungicide.

INTRODUCTION

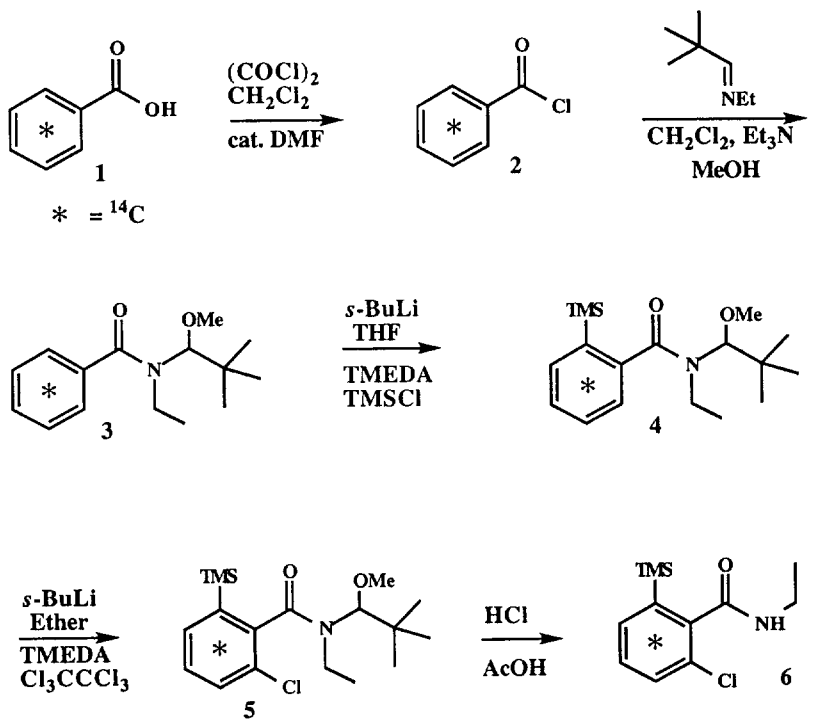
N-Ethyl-2-chloro-6-trimethylsilylbenzamide [Ring-14C(U)], **6**[1], has been found to effectively control Take-All disease in wheat. To complete environmental plant, animal and soil studies for registration, the synthesis of [^{14}C]-*N*-Ethyl-2-chloro-6-trimethylsilylbenzamide was required. This paper describes the synthesis and analysis of *N*-Ethyl-2-chloro-6-trimethylsilylbenzamide [Ring-14C(U)], **6**.

CCC 0362–4803/97/040267–07$17.50

Received 29 March 1996

RESULTS AND DISCUSSION

N-Ethyl-2-chloro-6-trimethylsilylbenzamide **6** was synthesized in five steps from uniformly labelled ^{14}C benzoic acid (Scheme). Benzoic acid **1** was converted to benzoyl chloride **2** in 100% yield using oxalyl chloride in CH_2Cl_2 at room temperature. Product **2** was converted to the protected *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide **3** with *N*-Ethyl-*tert*-butylmethyleneimine[3] and MeOH in CH_2Cl_2 at 0°C to give a 96% yield of *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide **3**. Product **3** was lithiated with *sec*-BuLi in THF at -78°C[4]. It was important that the lithiated species be cannulated into the TMSCl. Addition of the TMSCl to the lithiated species resulted in low yields of the silylated product **4**.



Scheme

Product **4** was prepared in 93% yield. Lithiation of **4** in ethyl ether[5] at -24°C with *sec*-BuLi was cannulated into a solution of hexachloroethane to produce **5** in nearly quantitative yield. The protecting group was easily removed using concentrated HCl in glacial AcOH at room temperature to produce the desired product, [^{14}C]-*N*-Ethyl-2-chloro-6-trimethylsilyl-benzamide. The final product was initially purified by recrystallization from hexanes. The recrystallized product was further purified by flash chromatography to give colorless crystalline material in 71% overall yield.

EXPERIMENTAL

Radioactivity was determined using Tracor Analytic Mark III counters which were interfaced with a Monsanto developed software package. Flash Column Chromatography was performed using Merck grade silica gel, 230-400 mesh, packed in 10% EtOAc / 90% hexanes. HPLC was performed using a Waters HPLC system consisting of a Model 680 Gradient Controller, two Model 510 pumps, a model U6K Injector, a Lambda-Max Model 481 UV detector set at 254 nm, a Packard Radiomatic Flo-One Beta radioactivity flow detector, and a Beckman Ultrasphere column, C18, 5 µm, 4.6 X 250 mm. GC-CIMS analysis was completed on a Finnigan model 4515 instrument using isobutane. All labelled compounds synthesized were identified by HPLC and/or TLC and/or MS comparison with the corresponding unlabelled material.

Benzoyl chloride [Ring-^{14}C(U)] 2. To an oven-dried flask under nitrogen was weighed benzoic acid **1** (0.4517 g, 3.70 mmol, 40.65 mCi/mmol, 150 mCi, NEN-DuPont). To this was added CH_2Cl_2 (4.3 mL),

oxalyl chloride (0.64 mL, 7.34 mmol) and DMF (10 μL) by syringe at room temperature. The reaction was stirred for 30 minutes and an additional catalytic amount of DMF was added. After 30 seconds no additional reaction was observed. The CH_2Cl_2 and excess oxalyl chloride were removed under reduced pressure to give benzoyl chloride **2**, (0.52 g, 100%) as a liquid which was used without further purification.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide [Ring-^{14}C(U)] 3.** To benzoyl chloride **2** (0.52 g, 3.7 mmol, 150 mCi) in CH_2Cl_2 (2.6 mL) was added a solution of *N*-Ethyl-*tert*-butylmethyleneimine (0.4336 g, 3.83 mmol) in CH_2Cl_2 (0.87 mL) dropwise over 2 minutes at 0°C. After 15 minutes, the ice bath was removed and the yellow solution was warmed to room temperature and stirred for 1.25 h. The solution was cooled to 0°C and Et_3N (0.54 mL, 3.9 mmol) was added followed by the dropwise addition of MeOH (0.28 mL, 6.9 mmol) over 10 minutes. The solution was warmed to room temperature and stirred for an additional 45 minutes. TLC analysis (SiO_2, 10% EtOAc / 90% hexanes, Rf 0.22) showed the labelled product matched that of the ^{12}C material. The reaction mixture was partitioned between Et_2O and saturated aq. $NaHCO_3$. The $NaHCO_3$ solution was extracted with 10 mL Et_2O. The combined Et_2O extracts were washed with saturated aq. $NaHCO_3$ (3 X 10 mL) and then dried over $MgSO_4$. Filtration and removal of Et_2O under reduced pressure gave a yellow oil, **3** (0.8873 g, 96%). Product **3** was used in the next step without further purification.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-trimethylsilylbenzamide [Ring-^{14}C(U)] 4.** To product **3** (0.88 g, 3.5 mmol, 142 mCi) in a 25 mL oven-dried flask with addition funnel under N_2 was added anhydrous THF (7.1 mL) and TMEDA (0.64 mL, 4.2 mmol). The solution was cooled to -78°C and *sec*-BuLi (3.56 mL, 4.63 mmol, 1.3 M in cyclohexane) was added dropwise over 20 minutes and then stirred for 70 minutes. The lithiated product was cannulated into a solution of TMSCl (0.67 mL, 5.28 mmol) in THF (3.5 mL) at -78°C over 15 minutes. After 15 minutes the solution was warmed to room temperature. The solution was partitioned between Et_2O and saturated aq. $NaHCO_3$. The $NaHCO_3$ solution was extracted with 15 mL ether. The combined ether extracts were washed with saturated aq. $NaHCO_3$ (3 X 10 mL) and then dried over $MgSO_4$. Filtration and removal of Et_2O under reduced pressure gave a yellow oil, **4** (1.0568 g, 93%). TLC analysis (SiO_2, 10% EtOAc / 90% hexanes) of the product showed the isolated material to have the same R_f value as authentic ^{12}C material (Rf = 0.50). The product was used in the next step without additional purification.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-trimethylsilylbenzamide [Ring-^{14}C(U)] 5.** To *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-trimethylsilylbenzamide, **4** (0.9568 g, 2.98 mmol) in Et_2O (6.1 mL) and TMEDA (0.59 mL, 3.91 mmol) at -78°C under nitrogen was added *sec*-BuLi (2.99 mL, 1.3 M in cyclohexane, 3.9 mmol) dropwise over 30 minutes. After stirring at -78°C for 15 minutes, the solution was warmed to -24°C in a dry ice-CCl_4 bath for 1 h. The reaction mixture was

transferred by canula into a solution of CCl_3CCl_3 (1.4123 g, 5.97 mmol) in 6.1 mL of Et_2O at -78°C over 10 minutes. The mixture was stirred at -78°C for 30 minutes and then allowed to warm to room temperature overnight. The reaction mixture was washed with 10% aq. HCl (3 X 10 mL) and was dried over $MgSO_4$. Filtration of the solution and removal of Et_2O under reduced pressure gave a yellow solid **5** (1.06 g, 100%). The product was contaminated with a small amount of CCl_3CCl_3. TLC analysis (SiO_2, 10% EtOAc / 90% hexanes) showed a spot with Rf 0.58 which matched that of authentic ^{12}C material. The material was used in the next step without further purification.

***N*-Ethyl-2-chloro-6-trimethylsilylbenzamide [Ring-^{14}C(U)]**

6. To a solution of **5** (1.06 g, 2.98 mmol) in glacial AcOH (7.9 mL) was added conc. HCl (0.80 mL, 9.7 mmol) dropwise at room temperature and the solution was stirred for 45 minutes. To the reaction mixture was added water (20 mL) and Et_2O (25 mL). After the layers were separated, the aqueous solution was extracted with Et_2O (15 mL). The combined ether extracts were washed with water (15 mL), saturated aq. $NaHCO_3$ (5 X 10 mL) and then dried over $MgSO_4$. Filtration and removal of the Et_2O under reduced pressure gave the final product, **6**. TLC analysis (SiO_2, 10% EtOAc / 90% hexanes) showed a spot with Rf 0.25 which matched that of authentic ^{12}C material. The product was recrystallized from hexanes and then was further purified by Flash Chromatography using 10% EtOAc / 90% hexanes to give 0.61 g (80%) of a colorless crystalline solid. A small portion was recrystallized from hexanes (mp 107°C). Analysis of the

product by HPLC showed the product to be 99% radiochemically pure (60% water / 40% acetonitrile, Isocratic, 2.0 mL/min, Retention time 11.6 minutes). Specific Activity was 42.01 mCi/mmol. GC/CIMS produced a spectrum consistent with a uniformly labelled phenyl ring. A molecular ion for the m+1 peak with a m/z ratio of 256 was present and isotope ions at 262, 264, 266 and 268 were observed.

ACKNOWLEDGEMENTS

The author thanks Robert Chott for analysis of intermediates and the final product by Mass Spectrometry.

REFERENCES AND FOOTNOTES

1. Phillion, D. P.; Braccolino, D. S.; Graneto, M. J.; Phillips, W. G.; Van Sant, K. A.; Walker, D. M.; Wong, S. C. (Monsanto Company) EP 538,231. A1; Chem. Abstr. 119: 160256 (1993).

2. For a review of Directed *ortho* Metalation reactions, see Snieckus, V. - Chem. Rev. 90: 879 (1990).

3. *N*-Ethyl-*tert*-butylmethyleneimine was prepared by reacting 70% Ethylamine with Trimethylacetaldehyde at 0-5°C. Distillation from Calcium hydride at 96-98°C produced the colorless oil in 88% yield.

4. For additional examples of Directed *ortho* Metalation reactions of *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamides, see Phillion, D.P. And Walker, D. M. - J. Org. Chem. 54: 8417 (1995).

5. Ether was used in place of THF since alkyl lithium species react with THF at higher temperatures. See Wakefield, B. J. - The Chemistry of Organolithium Compounds; Pergamon Press: Oxford, 1974. Wakefield, B. J. - Comprehensive Organic Chemistry; Barton, D., Ollis, W. D. Eds.; Pergamon Press: Oxford, 1979; Vol. 3, p 943ff.