SYNTHESIS OF HIGH SPECIFIC ACTIVITY 1,8-NAPHTHALIC ANHYDRIDE

Fred S. Tanaka, Ronald G. Wien and Barry L. Hoffer
U.S. Department of Agriculture*
Agricultural Research Service
Metabolism and Radiation Research Laboratory
Fargo, North Dakota 58105 U.S.A.

SUMMARY

The synthesis of [^{14}C-carboxyl] 1,8-naphthalic anhy-anhydride of high specific activity (31.8 mCi/mmol) is reported. The ^{14}C was introduced by carbonation of the Grignard reagent, 8-bromo-1-naphthylmagnesium iodide, that was prepared from 8-bromo-1-iodonaphthalene. The overall radiochemical yield for the reaction scheme was 63.7% based on barium carbonate-^{14}C.

Keywords: Herbicidal antidote, protectant, safener, radio-labeled synthesis, 1,8-napthalic anhydride.

INTRODUCTION

Chemicals that can reduce or eliminate the toxic effects of applied herbicides on crop plants have been called antidotes, protectants or safeners. Hoffman[1], a pioneer in the area of protectants, has identified over 1,800 herbicidal antidotes. One of the more promising antidotes for application in herbicidal usage is 1,8-naphthalic anhydride (1,8-NA). This antidote has been found to protect corn from EPTC[2,3], rice from molinate[4], corn coleoptiles from alachlor[5], wheat from barban[6], sorghum from alachlor and diallate[7], and corn, sorghum and cotton from cis-2,5-dimethyl-1-pyrrolidinecarboxanilide[8] injury. Reference sources[9,10] are

* Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture, and does not imply its approval to the exclusion of other products that may also be suitable.

0362-4803/84/060549-13$01.30

Received February 1, 1984
Revised March 15, 1984

available that describe in detail the effects of antidotes on herbicidal toxicities and references[11,12] are also available that provide chemical names and structures for the different herbicides cited.

The synthesis of ^{14}C-labeled 1,8-NA has been previously reported by Riden and Asbell.[13] Their synthetic scheme involved the reaction of 1,8-dibromonaphthalene with cuprous ^{14}C-cyanide; the resultant dinitrile was hydrolyzed to a diacid which was subsequently dehydrated to afford radiolabeled 1,8-NA. Experimental

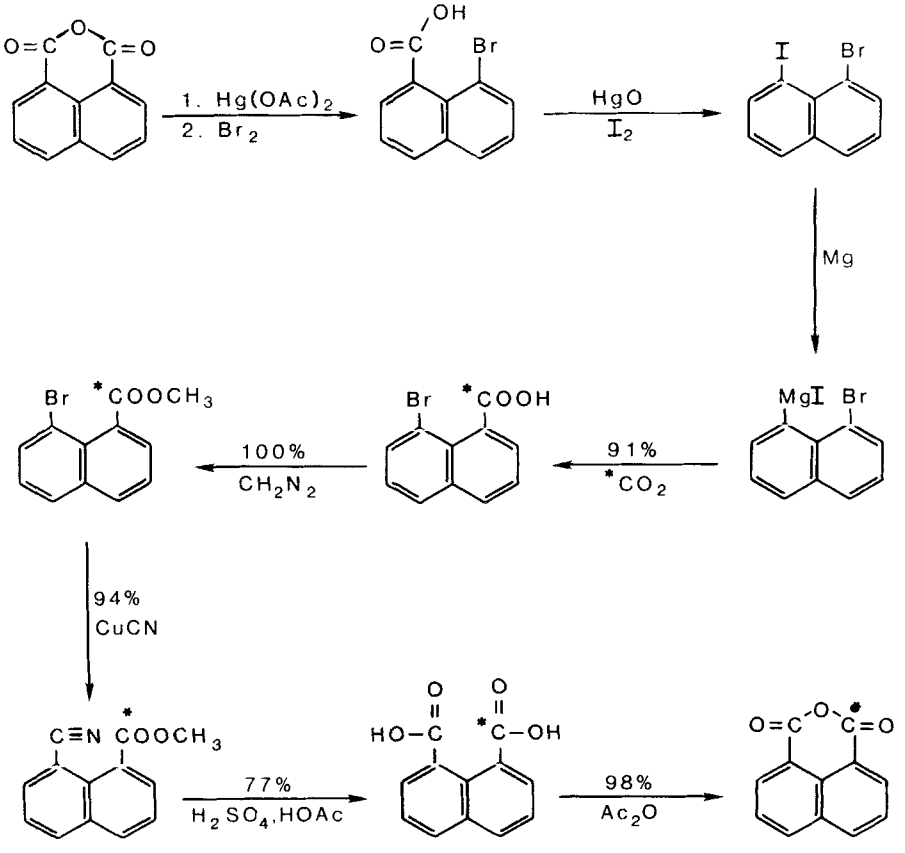

Figure 1.--Reaction scheme for the synthesis of [^{14}C-carboxyl] 1,8-naphthalic anhydride.

details and specific activity of product were not reported in their brief description of the synthesis. Their radioactive 1,8-NA was employed to follow its distribution in plants and soils. Since 1,8-NA has promise as a herbicidal antidote, the biological fate of this material should be investigated. For these studies, a product of high specific activity is required because only small amounts of material are used in seed treatments. We now report the preparation of ^{14}C-labeled 1,8-NA at high specific activity (Figure 1) that is suitable for biological fate studies.

EXPERIMENTAL

The 1,8-naphthalic anhydride was obtained from Aldrich Chemical and the ^{14}C barium carbonate (50 mCi) was purchased from New England Nuclear Corporation. Dry dimethylformamide was prepared by distillation from calcium hydride.

Melting points were determined with a Thomas-Hoover apparatus, and the observed melting points were reported uncorrected. Sonic agitation of samples was effected with a Branson B-12 ultrasonic cleaner. Liquid scintillation counting (LSC) was performed with a Packard 3375 spectrometer, and samples were counted in Instagel counting cocktail. The system for high-performance liquid chromatography (HPLC) was previously described[14] and separations were accomplished using a Waters Associates Radial-Pak CN cartridge.

The identity of each synthesized product was verified by HPLC and mass spectrometric data. All radioactive products showed identical retention times as authentic standards by HPLC and gave appropriate mass spectral molecular ions and fragmentation patterns in relation to authentic materials.

Yield measurements were accomplished by trapping purified products from the HPLC and counting the radioactivity from these fractions by LSC. Specific activity of the radioactive material was

TABLE 1

HPLC ANALYSIS OF REACTION PRODUCTS IN NAPHTHALIC ANHYDRIDE SYNTHESIS

Compound	Isocratic solvent system (v/v)	Retention time (min)
8-Bromo-1-naphthoic acid	CH_3CN/H_2O (1:1)	3.0
Methyl 8-cyano-1-naphthoate	CH_3CN/H_2O (1:1)	5.0
1,8-Naphthalic acid	CH_3CN/H_2O (3:7)	5.8
1,8-Naphthalic anhydride	CH_3CN/H_2O (3:7)	4.5

Column was Radial-Pak CN of 10 cm length, 5 mm diameter, and 10 μm sperical particles. Flow rate was 1 mL/min.

determined using the [^{14}C-carboxyl] methyl 8-cyano-1-naphthoate intermediate. This product was analyzed because it was completely separated by HPLC from its byproducts, it gave an excellent peak profile for sample trapping, and the authentic standard was a solid to allow accurate sample preparation. The specific activity of the cyano-intermediate and thus the final product, [^{14}C-carboxyl] 1,8-naphalic anhydride, was 31.8 mCi/mmol.

Synthesis of 8-Bromo-1-Naphthoic Acid.[15] A fresh solution of mercuric acetate was prepared by slowly dissolving red mercuric oxide (11 g, 51 mmol) in a mixture of glacial acetic acid (8 mL) and water (30 mL) at approximate boiling temperature. The hot solution was filtered and kept warm to avoid precipitation.

Disodium 1,8-naphthalate was prepared by dissolving 1,8-naphthalic anhydride (9.2 g, 46.4 mmol) in a warm stirred solution (240 mL) of 0.65 M sodium hydroxide. The warm solution was filtered and transferred into a 1-L, 3-necked flask equipped with heating mantle, reflux condenser and mechanical stirrer. The diso-

dium naphthlate was heated to gentle reflux and the warm mercuric acetate solution was added very slowly to prevent excessive foaming. After addition, the reaction was heated at gentle reflux for four days. To check for reaction completion, a test aliquot was completely dissolved in 2 N sodium hydroxide and a small piece of clean copper wire was added. The absence of mercury deposition on the wire indicated reaction completion. After heating was stopped, the product was allowed to precipitate from the stirred solution. The product obtained in approximate quantitative yield was filtered, washed with generous portions of water and 95% ethanol. Excess solvent was removed by suction, and the anhydro-8-hydroxymercuri-1-naphthoic acid was ready for preparation of the 8-bromo-1-naphthoic acid.

The moist hydroxymercuri-compound was transferred into a solution of glacial acetic acid (65 mL) and water (10 mL) and placed into suspension with stirring. The suspension was cooled in ice, and a chilled solution of bromine (2.4 mL) in 33 mL of concentrated aqueous sodium bromide (ca. 8 M) was slowly added with stirring. The yellow suspension was stirred for an additional 30 min and then slowly warmed to 90 °C. Then 450 mL of hot water was added and the reaction mixture was boiled for 10 min. The hot solution was filtered using vacuum, and the product was allowed to precipitate as the filtrate cooled. The crude product (5.2 g, 66% yield) melted at 168-172 °C. The product when recrystallized from benzene (4 g, 51% yield) melted at 175-177 °C (Lit. mp 177 °C).[16]

Synthesis of 8-Bromo-1-Iodonaphthalene.[17] A solution of 8-bromo-1-naphthoic acid (5 g, 20 mmol) was prepared by heating and stirring the acid in 250 mL of 1,1,1-trichloroethane. At the same time, an iodine solution (5.1 g, 20 mmol) was prepared in 250 mL of trichloroethane. After the bromonaphthoic acid had completely

dissolved, the iodine solution was added, and the reaction was brought to reflux. The red mercuric oxide powder (2.2 g, 10 mmol) was added in small portions and the reaction was allowed to reflux until the mixture changed from purple to red-orange in color. Generally the color change occurred in 3 to 4 h. The reaction was cooled, filtered, and the trichloroethane was removed by rotary vacuum evaporation.

The residue was dissolved in benzene, filtered and partitioned successively against 50 mL of aqueous 5% potassium iodide (2X), 50 mL of aqueous 5% sodium hydroxide (2X) and 50 mL of distilled water. The benzene layer was separated and dried over anhydrous magnesium sulfate. After drying, the benzene was removed and the residue was dissolved in benzene:n-hexane (9:1 v/v). Initial purification was accomplished on a 20 mm x 100 cm column of silica gel powder (60-200 mesh) using benzene:hexane (9:1) as the eluting solvent. The product was eluted in the first 100 mL of column effluent (4 g, 60% yield). The 8-bromo-1-iodonaphthalene after recrystallization from 95% ethanol had a melting point of 96-97 °C (Lit. mp 99-100 °C).[16]

Synthesis of 8-Bromo-1-Naphthylmagnesium Iodide. For preparation of the Grignard reagent[18], a 100-mL 3-necked round-bottom flask was charged with 8-bromo-1-iodonaphthalene (1.33 g, 3.67 mmol), anhydrous diethyl ether (10 mL), and magnesium turnings (300 mg, 12.3 mmol). The reaction vessel was equipped with nitrogen inlet, mechanical stirrer, and reflux condenser with drying tube. The reaction was started by adding a minute crystal of iodine. While being stirred under an atmosphere of nitrogen, the reaction was heated at gentle reflux for about 3 h. The Grignard reagent was transferred into an addition funnel, and 15 mL of anhydrous diethyl ether was added to prevent solidification of the Grignard reagent during transfer into the carbonation apparatus.

Synthesis of [^{14}C-Carboxyl] 8-Bromo-1-Naphthoic Acid. A carbonation apparatus was previously reported for the addition of an alkyl lithium reagent (-107 °C) to solidified $^{14}CO_2$.[19] This apparatus was modified (Figure 2) with two oblique-bore, high-vacuum stopcocks to afford a closed system that would allow for the addition of a Grignard reagent at room temperature to solidified $^{14}CO_2$.

The radioactive barium carbonate (44.3 mCi, 209.6 mg, 1.06 mmol) was transferred into the generating flask (D), and the system was evacuated to about 0.1 mm. Stopcock J was closed and stopcock

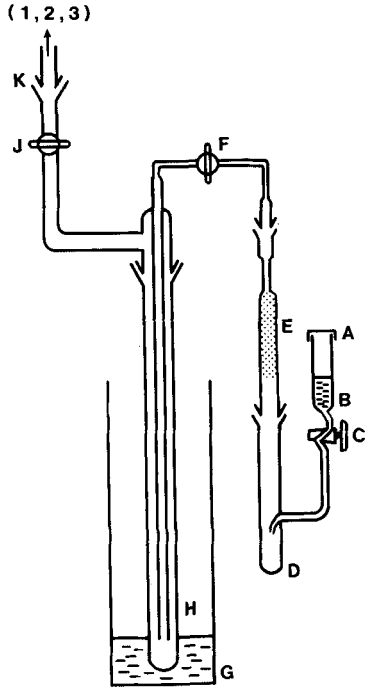

Figure 2.--Apparatus for carbonation of the Grignard reagent. A, rubber septum; B, 40% perchloric acid; C, stopcock; D, CO_2 generation flask; E, anhydrone; F, stopcock; G, liquid nitrogen bath; H, CO_2 trap; J, stopcock; K, ground glass connection for: 1) high vacuum pump; 2) Grignard reagent in addition funnel with drying tube protection; 3) washing tower (1 M NaOH) and low vacuum pump.

F was opened and the $^{14}CO_2$ was slowly released using 1 mL of 40% perchloric acid.[19] The generated $^{14}CO_2$ was transferred by vacuum into the cold trap (H) which contained a fine wadding of glass wool to assist in condensation of the $^{14}CO_2$. Using a hypodermic needle, a small amount of nitrogen was bled through serum cap A to sweep residual $^{14}CO_2$ into the cold trap. Stopcock F was closed, the high vacuum line was removed, and an addition funnel protected by a calcium chloride drying tube was fitted at K. The ethereal solution of 8-bromo-1-naphthylmagnesium iodide in the addition funnel was added in small portions into the cold trap via stopcock J. Each aliquot was allowed to freeze before a second addition was made. After the Grignard reagent was completely added, stopcock J was closed, the liquid nitrogen bath was removed, and the reaction was allowed to stand at room temperature overnight with occasional agitation by sonication.

Then a low vacuum pump fitted to a washing tower containing 1 N sodium hydroxide was attached at K. All stopcocks were opened, and nitrogen was bled through serum cap A via a hypodermic needle. Thus, the unreacted $^{14}CO_2$ was swept under low vacuum from the reaction vessel into the sodium hydroxide trap. Methanol was then added to decompose the material in the reaction mixture. Enough methanol was added to afford a finely divided precipitate after sonic agitation. Then 74 mg of 8-bromo-1-naphthoic acid was added as carrier material to the reaction vessel. The reaction was filtered through a sintered glass funnel using celite filter aid, and the precipitate was washed well with methanol. The filtrate was reduced to dryness and redissolved in an excess of water-washed dichloromethane. This dichloromethane fraction was passed through filter aid and the precipitate was washed well with additional water-washed dichloromethane (Yield 90.6%, 40.1 mCi, 1.26 mmol).

A buffered silica gel column[20] was employed to purify the pro-

duct. The column was prepared by packing a 50-mL buret with about 35 mL of buffered silica gel suspended in water-washed dichloromethane. The radioactive product was placed on-column in 200 mL of water-washed dichloromethane and the column was eluted with an additional 150 mL of water-washed dichloromethane. Then the 8-bromo-1-naphthoic acid was eluted from the column with 180 mL of diethyl ether. The ether fraction was reduced to dryness; product recovery was estimated at 99% (39.7 mCi, 1.25 mmol).

Synthesis of Methyl 8-Bromo-1-Naphthoate-^{14}C. The 8-bromo-1-naphthoic acid (39.7 mCi, 313.5 mg, 1.25 mmol) was dissolved in 5 mL of anhydrous diethyl ether and treated with 10 mL of freshly prepared diazomethane.[21] The diazomethane was slowly added to the carboxylic acid until the yellow color persisted. This solution was stirred for 30 min and the excess diazomethane was destroyed by warming (yellow color disappears). After the ether was removed, the product was dried in a dessicator overnight (Yield 100%, 331 mg).

Synthesis of Methyl 8-Cyano-1-Naphthoate-^{14}C. Cuprous cyanide[22] was prepared in a 500-mL, 3-necked, round-bottom flask fitted with mechanical stirrer, addition funnel and gas exit tube leading to the hood flue. Crystalline cupric sulfate (32.5 g, 0.13 mol) was dissolved in 200 mL of water. While this solution was stirred and heated at 80 °C, 35 mL of aqueous sodium cyanide (12.8 g, 0.26 mol) was added over a 30 min period. To remove the byproduct, cyanogen, the solution was boiled for about 10 min. After the product had settled, the reaction was decanted and then filtered. The freshly prepared cuprous cyanide was washed with water, methanol and diethyl ether before drying at 110 °C for 36 h.

A mixture of methyl 8-bromo-1-naphthoate (39.7 mCi, 331 mg, 1.25 mmol), cuprous cyanide (310 mg, 3 mmol) and dry dimethylform-

amide (10 mL) was stirred at gentle reflux for 4 h.[23] The resulting brown mixture was cooled to 65 °C and treated with 5 mL ferric chloride solution; this solution was composed of hydrated ferric chloride (4 g), 12 N hydrochloric acid (1 mL) and water (6 mL). The mixture was heated at about 65 °C for 30 min to decompose the complex. Then 100 mL of distilled water was added and the reaction was extracted (3X) with 75-mL portions of diethyl ether. The ether was evaporated to afford the product in 93.9% yield (37.3 mCi, 236 mg, 1.12 mmol).

Synthesis of 1,8-Naphthalic Acid-^{14}C. Methyl 8-cyano-1-naphthoate (37.3 mCi, 236 mg, 1.17 mmol), glacial acetic acid (5 mL) and 18 N sulfuric acid (10 mL) were stirred into solution, placed under a nitrogen atmosphere, and heated at 130 °C for 7 days.[24] Then the acetic acid was volatilized from the hot solution with a stream of nitrogen, and the product was precipitated by addition of about 50 g of crushed ice. The precipitated product was filtered, washed with cold water, and dried. The filtrate was extracted (3X) with 50-mL portions of diethyl ether for recovery of additional product. This extract was reduced to dryness and combined with the precipitate (yield 76.9%, 28.7 mCi, 195 mg, 0.90 mmol).

Synthesis of 1,8-Naphthalic Anhydride-^{14}C. Acetic anhydride (5 mL) was added to the 1,8-naphthalic acid (28.7 mCi, 195 mg, 0.90 mmol) and the mixture was heated at gentle reflux for 1 h under a nitrogen atmosphere.[25] To allow for escape of the acetic acid that was produced, an air condenser was employed. In the workup excess acetic anhydride was removed by rotary vacuum evaporation using dry toluene to aid in distillation (yield 98%, 28.2 mCi, 176 mg, 0.89 mmol).

Purification of 1,8-NA-^{14}C. Initial purification of the radioactive 1,8-NA was accomplished on anasil HF plates (Analabs) of

0.25 mm thickness using dichloromethane as the developing solvent (R_f 0.7). The product was eluted from silica gel, filtered and then purified by HPLC (Table 1). The purified product was homogeneous upon examination by thin-layer chromatography followed by autoradiography.

DISCUSSION

The reaction of 1,8-dibromonaphthalene with cuprous cyanide to afford the dinitrile in 80.3% yield was recently reported.[26] In this reaction, cuprous cyanide was used in 25% excess and the yield was based on dibromonaphthalene. Thus, to employ this reaction for radiochemical synthesis, it would be necessary to convert the readily available $Na^{14}CN$ into $Cu^{14}CN$ on a micro scale; hence, the yield for conversion would be considerably lower than the 85-90% reported for macro scale synthesis.[22] Furthermore, the $Cu^{14}CN$ would have to be used in molar excess to achieve dinitrile formation in good yield. Therefore, we decided to develop our synthetic approach based on $^{14}CO_2$ rather than on the previously reported concept of $Cu^{14}CN$.[13]

In Grignard reagent synthesis, the reaction of magnesium with dibromonaphthalene[16] was reported to occur only at very slow rate. For this reason, we had hoped to prepare the more reactive diiodonaphthalene from 1,8-diaminonaphthalene via the Sandmeyer reaction. This reaction, however, produced extremely low yields and the product could not be readily purified. Therefore, our radiochemical synthesis was conducted with bromoiodonaphthalene and ^{14}C was introduced into just one carbonyl group of 1,8-NA. The possibility of formation of any di-Grignard reagent from bromoiodonaphthalene was considered not to be of any significance because of the slow reaction rate reported for magnesium and dibromonaphthalene.

Finally, the labeling of both carbonyls was not deemed necessary because the structural symmetry of 1,8-NA makes the two carbonyl groups chemically equivalent.

The molar ratio of Grignard reagent to CO_2 required for maximum yield in micro carboxylation reactions was investigated by Van Bruggen et al.[27] In their study, yields did not increase after Grignard reagent to CO_2 molar ratios were increased beyond 5:1. For this synthesis, a molar ratio of about 4:1 was used to avoid using large volumes of solvent because our Grignard reagent was of low solubility in diethyl ether.

After the introduction of ^{14}C via the carbonation reaction, the radioactive product was purified using a buffered silica gel column. Only partial purification of all subsequent reactions was accomplished by means of extraction and/or filtration. Thus, chemical compounds of similar nature with reaction products could be carried on to subsequent reactions. Therefore, in the assay of the final reaction mixture by TLC, HPLC, LSC, and mass spectrometry, 3 mCi of unhydrolyzed 8-cyano-1-naphthoic acid and 2 mCi of 1,8-naphthalimide (the carbimino analog may also be present) resulting from partial hydrolysis of cyanonaphthoic acid were present. If additional product was desired, this material (5 mCi) could be recycled through the hydrolysis step to afford additional 1,8-naphthalic acid for 1,8-NA synthesis.

REFERENCES

1. Hoffman, O.L. - Abstracts of Papers, 173rd National Meeting of the American Chemical Society, New Orleans, LA, Mar. 1977, American Chemical Society, Washington, D.C. (1977), PEST 61.

2. Riden, J.R. - Analytical Methods for Pesticides and Plant Growth Regulators, Vol. VIII, Academic Press, New York (1976), p. 483.

3. Murphy, J.J. - Chem.-Biol. Interactions 5: 284 (1972).

4. Arneklev, D.R. and Pallos, F.M. - Stauffer Chemical Co., U.S. Patent 4,197,111.

5. Hickey, J.S. and Krueger, W.A. - Weed Sci. 22: 250 (1974).

6. Hoffman, O.L. - Weeds 10: 322 (1962).

7. Jordan, L.S. and Joliffe, V.A. - Bull. Environ. Contam. and Toxicol. 6: 417 (1971).

8. Holm, R.E. and Szabo, S.S. - Weed Research 14: 119 (1974).

9. Hoffman, O.L. - Chemtech 8: 488 (1978).

10. Pallo, F.M. and Casida, J.E., Eds. - Chemistry and Action of Herbicide Antidotes, Academic Press, New York (1978).

11. WSSA - Herbicide Handbook of the Weed Science Society of America, 4th ed., Humphrey Press, Geneva, New York (1979).

12. Frear, D.E.H. - Pesticide Handbook - Entoma, College Science Publishers, State College, PA (1968).

13. Riden, J.R. and Asbell, W.J. - Environ. Qual. Saf. Suppl. 3 (pesticides): 175 (1975).

14. Tanaka, F.S., Wien, R.G. and Hoffer, B.L. - J. Agric. Food Chem. 29: 1153 (1981).

15. Rule, H.G., Pursell, W. and Brown, R.R.H. - J. Chem. Soc. 168 (1934).

16. Fieser, L.F. and Seligman, A.M. - J. Am. Chem. Soc. 61: 136 (1939).

17. Davis, J.A., Herynk, J., Carroll, S., Bunds, J. and Johnson, D. - J. Org. Chem. 30: 415 (1965).

18. Gilman, H., St. John, N.B. and Schulze, F. - Organic Syntheses, Coll. Vol. II, Wiley, New York (1959), p. 425.

19. Tanaka, F.S. and Wien, R.G. - J. Labelled Compds. Radiopharm. 12: 41 (1976).

20. Blanchard, F.A., Muelder, W.W. and Smith, G.N. - J. Agric. Food Chem. 8: 124 (1960).

21. de Boer, T.J. and Backer, H.J. - Organic Syntheses, Coll. Vol. IV, Wiley, New York (1963), p. 250.

22. Supniewski, J.V. and Salzberg, P.L. - Organic Syntheses, Coll. Vol. I, Wiley, New York (1961), p. 46.

23. Friedman, L. and Schecter, H. - J. Org. Chem. 26: 2522 (1961).

24. Whitmore, F.C. and Fox, A.L. - J. Am. Chem. Soc. 51: 3363 (1929).

25. Nicolet, B.H. and Bender, J.A. - Organic Syntheses, Coll. Vol. I, Wiley, New York (1961), p. 410.

26. Chang, S.-J. - Synth. Comm., 12: 673 (1982).

27. Van Bruggen, J.T., Claycomb, C.K. and Hutchens, T.T. - Nucleonics, 7(3): 45 (1950).