3-(1,2-DIPHENYLETHYL)-1,4,5,6-TETRAHYDRO-1,2,4-TRIAZINE-3-^{14}C MONOHYDROCHLORIDE

Lennon H. McKendry
The Dow Chemical Company
Midland, Michigan 48640

SUMMARY

3-(1,2-Diphenylethyl)-1,4,5,6-tetrahydro-1,2,4-triazine-3-^{14}C hydrochloride(6) with a specific activity of 25.53 mCi/mmole was prepared in a 66.1% yield from benzyl cyanide-1-^{14}C via a three step process.

Key Words: (3-(1,2-Diphenylethyl)-1,4,5,6-tetrahydro-1,2,4-triazine-3-^{14}C monohydrochloride), Carbon-14, 3-aralkyl-as-triazines, 2,3-diphenylacryonitrile-1-^{14}C, 2,3-diphenylpropionitrile-1-^{14}C

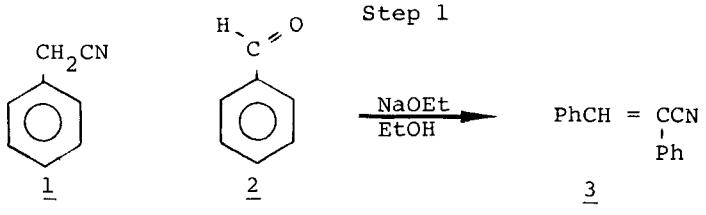
INTRODUCTION

3-(1,2-Diphenylethyl)-1,4,5,6-tetrahydro-1,2,4-triazine hydrochloride(6) is an antidepressant(1,2) currently undergoing clinical trials. A radiolabeled sample was required for pharmacokinetic and metabolism studies in monkeys.

DISCUSSION

The series of reactions used to produce 6 are given in Scheme I.

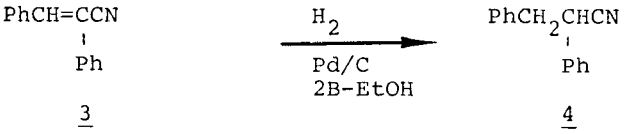
SCHEME I



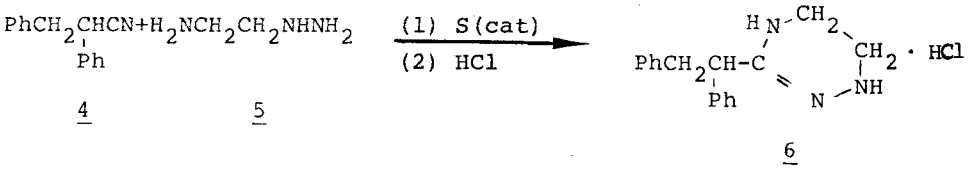
0362-4803/80/0117-0043$01.00

Received December 10, 1978
Revised January 22, 1979

Step 2



Step 3



Initially non-radioactive reactants were used (cold runs) to adapt the reaction sequence to microsynthetic conditions. The first two steps of the sequence proceeded smoothly affording a 94.8% overall yield of 2,3-diphenylpropionitrile (98.8 GLC area % pure) purified *via* silica gel chromatography. Duplication of the reaction sequence using phenylacetonitrile-1-^{14}C afforded a 76.3% yield of radiolabeled 4. The product was 99.4 GLC area % pure and no impurities could be detected by TLC. The differences in the yields of 4 are a result of the difference in the yield of crude 3 isolated, being only 83% in the latter instance.

Considerable difficulty was initially encountered in Step 3 of the reaction(3). The lack of reaction of 3 and 4 under atmospheric conditions was attributed to the loss of the volatile catalyst (3) derived from the sulfur under microsynthetic conditions. Therefore, the reaction was conducted under sealed ampoule

conditions. The latter technique afforded an 83.0% yield of 6 in the cold run, mp 231-233°C. The infrared spectrum (nujol) and mass spectrum (obtained by W. Braun, Dow Chemical) of the product were identical to those of authentic 6, mp 231-233°C.

Repetition of Step 3 (Scheme I) with 2,3-diphenylpropionitrile-1-^{14}C afforded an 86.7% yield (66.1% overall yield) of >99% radiochemically pure 3-(1,2-diphenylethyl)-1,4,5,6-tetrahydro-1,2,4-triazine-3-^{14}C hydrochloride.

GLC ANALYSES

All GLC analyses were conducted on a Hewlett Packard Model 5830A instrument containing a 2' x 4 mm glass column packed with 10% SE 30 on Chromasorb WHP, 80-100 mesh; Conditions: A(For Step 1 of Scheme I) 50-250°C at 20°/min, time at 50°=2.0 min, time at 250°=7.0 min; B (For Steps 2 and 3) 100-250°C at 20°/min, time at 100°=2.0 min, time at 250°C=7.0 min. The following retention times were observed:

Component	Conditions	Rt(min)
1	A	5.95
2	A	4.50
3	A	11.04
3	B	8.48
4	B	7.63
6	B	10.77

EXPERIMENTAL

2,3-Diphenylacryonitrile-1-^{14}C (3)

The ampoule containing benzyl cyanide-1-^{14}C (New England Nuclear, Lot #922-187, Assay #90450, 20.0 mCi, 24.8 mCi/mmole, 0.806 mmole) was opened and the contents transferred to a 25-ml pear-shaped flask previously flushed with N_2. The ampoule was rinsed with 14-0.5 ml-portions of 2B-ethanol (contains 2% benzene) and the rinses added to the flask. Benzaldehyde, 97 µl, (0.960 mmole) was added to the resultant solution. Sodium, 230 mg (10.0 mmole), was dissolved in 10 ml of 2B-ethanol in a volumetric flask and a 0.81 ml sample of the resultant solution (0.81 mmole) added dropwise to the above solution under a N_2 atmosphere over a ca 2 minute period. The flask was stoppered and stirring continued at ca 22°C for 2.0 hours. An additional 4.0 µl (0.0396 mmole) of benzaldehyde and 0.3 ml of the above NaOEt solution were added and stirring continued for 0.67 hours. A final 8 µl of benzaldehyde was added causing the last of the benzyl cyanide (GLC analysis) to react. After stirring for 1.0 hour, the solution was cooled in an ice bath and 7 ml of H_2O added dropwise. The resultant mixture was stirred 0.5 hour and most of the solvent removed from the precipitate using a pipette containing a glass wool plug. The concentrated mixture was filtered, and the precipitate washed with 1:1 2B-ethanol-H_2O solution. The precipitate was dissolved in 2 ml of CH_2Cl_2 and filtered through $MgSO_4$ into a 25 ml round

bottomed flask. The original flask and filter were rinsed with 10-0.5 ml-portions of CH_2Cl_2 and the rinses transferred to the 25 ml flask. The solvent was removed under a N_2 stream to afford 137.3 mg of light yellow crystalline 2,3-diphenylacryonitrile-1-^{14}C(3) (Theory = 165.4 mg, 83% yield). The precipitate was dissolved in 2 ml of 2B-ethanol and transferred to a 25 ml round bottomed 2-neck (14/20 and 19/22 ℠ joints) flask and the original flask rinsed with 8-0.5 ml-portions of 2B-ethanol. The final solution contained no detectable impurities by GLC.

The cold run under the above conditions afforded a 97% yield of crude 3.

2,3-Diphenylpropionitrile-1-^{14}C (4)

The flask containing the above 2-B ethanol solution of 3 was connected to a hydrogenation system, flushed with N_2 and a small quantity of 5% Pd/C added. The system was flushed with H_2 and the hydrogenation initiated. After 3.1 hours of stirring at ca 22°C, 25 ml (ca 1.1 mmole) of H_2 had been consumed and the reaction was >99.7% complete by GLC analysis. The mixture was filtered through Celite filter aid and the solvent removed from the filtrate in vacuo. The crystalline residue was dissolved in 2 ml of 1:9 (v/v) acetone:n-hexane and chromatographed on a 3.0 cm x 45 cm column containing 100 g of Brinkmann Silica Gel G60 with 1:9 acetone:n-hexane solution to afford upon solvent removal

127.5 mg (0.615 mmole, 92.0% yield, 76.3% overall yield) of 4 as a white crystalline solid (99.4 GLC area % pure). The precipitate was dissolved in 1 ml of Et_2O and a sample spotted on a 2" x 8" Silica Gel 60-F254 plate. The plate was developed with 1:9(v/v) acetone:n-hexane and scanned on a Vanguard autoscanner. No radioactive impurities were detected.

3-(1,2-diphenylethyl)-1,4,5,6-tetrahydro-1,2,4-triazine-4-^{14}C monohydrochloride (6)

The above ethereal solution of 4 was transferred to a ca 15 ml glass ampoule, the flask rinsed with several portions of Et_2O, and each rinse transferred to the ampoule. Sulfur, 1.4 mg (0.0438 mmole, 7.1 mole %) was added and the Et_2O removed under a N_2 atmosphere. The flask was cooled to -78°C and a 200 µl aliquot (2.66 mmole, 4.33 eq) of distilled 2-aminoethylhydrazine (bp 38°/0.2 mm) was added under a N_2 atmosphere. The ampoule was sealed, wrapped in glass wool, placed in a S.S. tube half filled with CH_2Cl_2 and the tube sealed and placed in a 95°C oil bath. After 24 hours the tube was cooled in an ice bath, the ampoule removed, cooled to -78°C and opened. The contents were allowed to warm to ca 22°C under a N_2 atmosphere and transferred to a 25 ml pear shaped flask containing a side arm and previously flushed with N_2. The ampoule was rinsed with 5-0.5 ml-portions of C_6H_6, 5-0.5 ml-portions of H_2O and finally with 5-0.5 ml-portions of

C_6H_6. The combined mixture was stirred well and the aqueous layer removed. The organic layer was washed with 5 ml of H_2O, dried (Na_2SO_4), and the filtrate collected in a 10 ml pear shaped flask. The filtrate was cooled in an ice bath and 0.6 ml of a previously prepared 2B-ethanol-HCl solution (0.998 mmole HCl/ml) was added dropwise. The first few drops cause cloudiness but a clear solution results upon complete addition. The solution was stirred 0.5 hours at ca 5°C affording a white precipitate. The mixture was filtered and the precipitate washed with two-0.5 ml-portions of C_6H_6 and two-0.5 ml-portions of 1:1 (v/v) isopropanol:n-hexane solution. The precipitate was dissolved in MeOH and transferred to a 100 ml volumetric flask. The filter was rinsed with several portions of MeOH and the solution diluted to volume (Solution A). A 1 µl aliquot of Solution A was analyzed by GLC to afford a spectrum identical to that for analytically pure 6 (obtained from G. Hurst, Dow Chemical).

A 1.0 ml aliquot of Solution A was diluted to 100 ml (Solution B) and a 1 ml aliquot of Solution B diluted to 10 ml (Solution C).

A 0.5 ml aliquot of Solution A was removed for subsequent radiometric analyses and the solvent removed from the remaining 98.5 ml of solution in vacuo to afford 158.4 mg (0.5248 mmole, 86.7% yield, 66.1% overall yield) of >99% radiochemically pure 6 (13.52 mCi total at 25.53 mCi/mmole).

RADIOMETRIC DETERMINATION

The radioactivity was determined in a Packard Tri-Carb Liquid Scintillation Spectrometer using New England Nuclear Aquasol universal liquid scintillation cocktail. Triplicate assays of Solution C were taken.

The radiochemical purity was determined by spotting 2 µl aliquots of Solution A on seven 2" x 8" Silica Gel 60 F254 plates along with standard samples of 6 and intermediate 4 and developing the plates in (A) 1:1(v/v) C_6H_6:CH_3OH (B) 3.5:1.5:1(v/v/v) CH_3CN:CH_3OH:HCO_2H (C) 30:10:1(v/v/v) $CHCl_3$:CH_3OH:NH_4OH (D) 4:1(v/v) CH_3CN:HCO_2H (E) 5:5:1(v/v/v) C_6H_6:CH_3OH:HCO_2H (F) 5.3:1(v/v) C_6H_6:Et_3N and (G) 10:10:1(v/v/v) C_6H_6:iPrOH:CF_3CO_2H.

The plates were photographed by exposing them to Kodak Medical X-Ray film (RP Royal X-Onat) over a 16 hour period. Plates A and F possessed considerable tailing whereas decomposition appeared to be occurring on Plate G. Plates D and E were scraped in 5 mm sections using a Zonal Scraper and each section deactivated with 50% aqueous methanol, diluted with Aquasol and counted. Histogram analyses of the data afford product of >99% radiochemical purity.

REFERENCES

1. Trepanier D. L., Shriver K. L., and Eble J. N. - J. Med. Chem., 12 257(1969).

2. Trepanier D. L. - U.S. Patent 3,471,485 (1969).

3. Schuster, A. J. and Martin J. - U. S. Patent 4,071,684(1978).