SYNTHESIS OF 1-PHENYL-2-PHENYL-1-^{13}C-ETHENE-1-^{13}C (TRANS-STILBENE) AND DERIVATIVES

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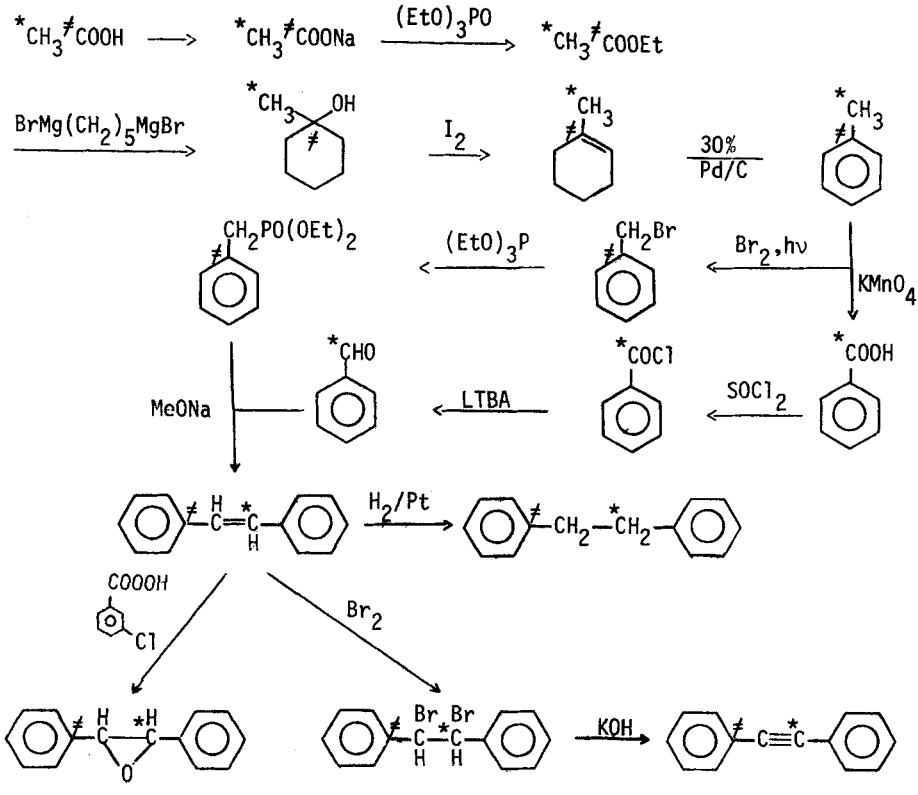
SUMMARY

For mass spectrometric studies 1-phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C (trans-stilbene) was synthesized from acetic-1-^{13}C acid and acetic-2-^{13}C acid *via* methylcyclohexene-1-^{13}C and -α-^{13}C and toluene-1-^{13}C and -α-^{13}C. No scrambling of the label was observed during the aromatization step. The labeled stilbene was converted into 1-phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C (bibenzyl), 2-phenyl-3-phenyl-1-^{13}C-oxirane-2-^{13}C (trans-stilbene oxide), meso-1,2-dibromo-1-phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C and 1-phenyl-2-phenyl-1-^{13}C-ethyne-1-^{13}C (tolan).

Key Words: Mass Spectrometry, trans-Stilbene, Aromatization

Several mass spectrometric studies have been reported involving the rearrangement of trans-stilbene under electron impact. They have been directed in particular to the ion generated by loss of methyl (M-15). In order to study the rearrangement of trans-stilbene and derivatives we have looked at the carbon scrambling of the M-15 ion, the C_8 unit (loss of phenyl), the C_7-unit (loss of C_7) and the phenyl ion (loss of C_8). Possible scrambling patterns are (1) total scrambling (2) scrambling of the two bridge carbons, (3) scrambling within the C_2 unit, and (4) scrambling within the phenyl unit. In order to compare our mass spectrometric results with statistically calculated data for the various scrambling patterns we needed unsymmetrically ^{13}C-dilabeled stilbene and bridge transformation products therefrom. Starting with 1- and 2-labeled acetic acid

it was found convenient to synthesize the six membered ring via a Grignard reaction with 1,5-dibromopentane.[2,3] This yielded 1- and α-labeled 1-methylcyclohexanol. Dehydration followed by aromatization[4] provided toluene-1-^{13}C and -α-^{13}C. Since the aromatization over palladium on charcoal was carried out at 400° the danger of scrambling of the label had to be envisaged. However, it could be clearly shown by ^{13}C-nmr that the label in the toluene remained in position. Toluene-1-^{13}C was converted via benzyl-1-^{13}C bromide into benzyl-1-^{13}C diethylphosphonate[5] and toluene-α-^{13}C was converted via benzoyl-carbonyl-^{13}C chloride into benzaldehyde-formyl-^{13}C. The benzyl diethylphosphonate and benzaldehyde were coupled to yield 1-phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C (trans-stilbene).[7] The various derivatives of stilbene were obtained by catalytic hydrogenation[8] (1-phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C), epoxidation[9] (2-phenyl-3-phenyl-1-^{13}C-oxirane-2-^{13}C) bromination (meso-1,2-dibromo-1-phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C) and dehydrobromination of the latter compound[10] (1-phenyl-2-phenyl-1-^{13}C-ethyne-1-^{13}C).



EXPERIMENTAL

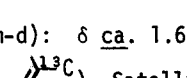
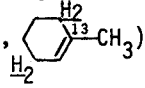
Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Nmr spectra were recorded on a Varian EM360 spectrometer. Mass spectra were recorded on a DuPont 21-491 spectrometer. Solvents and other chemicals used were all A.R. grade. The two mono-labeled acetic acids were prepared at the Los Alamos Scientific Laboratory.[1]

Sodium Acetate-1-^{13}C (90.00% ^{13}C). A solution of 2.00 g (0.033 mole) of acetic-1-^{13}C acid (90.00% ^{13}C) in 15 ml distilled water was titrated to a phenolphthalein endpoint with 1.0 N sodium hydroxide solution. Water was removed by roto-evacuation. The resulting pinkish crystals were dried at 140° and 0.1 torr for three hours, yielding 2.71 g (99.5%) of sodium acetate-1-^{13}C, mp 328-328.5° (reported[11] 324°).

Ethyl Acetate-1-^{13}C (90.00% ^{13}C). Sodium acetate-1-^{13}C was powdered, 10 ml of triethyl phosphate and a piece of glass wool were added, the mixture was heated under reflux to 170°-210° for three hours. The mixture was distilled using a liquid nitrogen-cooled receiver at 0.1 torr, yielding 2.89 g (99.5%) of ethyl acetate-1-^{13}C. Nmr (chloroform-d): δ 1.23 (t,3H,J = 7 Hz, $C\underline{H}_3CH_2O$-), 2.00 (s/d,3H,J = 5.6 Hz, $C\underline{H}_3$-^{13}CO-), 4.0 (q,2H,J = 7 Hz, $CH_2\underline{C}H_3$).

Methylcyclohexene-1-^{13}C (90.00% ^{13}C). Into a 250 ml three-necked round bottom flask fitted with magnetic stirrer, reflux condenser, $CaSO_4$ drying tube, and addition funnel was placed 4.97 g (0.204 mole) of magnesium turnings and a crystal of iodine. Ten ml of a solution containing 22.38 g (0.097 mole) of 1,5-dibromopentane and 122 ml of anhydrous ether was added quickly to the flask while stirring vigorously. As soon as the ether began to reflux the rest of the solution was added over a half hour period, and the mixture was stirred at room temperature for an additional one and one-half hours. A solution of 2.89 g (0.032 mole) of acetate-1-^{13}C in 34 ml of anhydrous ether was added dropwise while vigorously stirring and cooling the reaction mixture in an ice bath. After the addition was complete the ice bath was removed and the stirring was continued overnight. The reaction mixture was refluxed one hour,

cooled in ice, and 20 ml of saturated ammonium chloride solution was slowly added while vigorously stirring. The two layers were separated and the aqueous layer was extracted twice with 50 ml portions of ether. The ether fractions were combined, washed with water until neutral, dried ($MgSO_4$), and the ether was evaporated leaving a viscous residue of 1-methylcyclohexanol-1-^{13}C and a high boiling compound which was not identified. The 1-methylcyclohexanol was isolated once to determine its actual presence.

A crystal of iodine was added and the mixture was heated to 140-145° for two hours. The product was codistilled with water into a liquid nitrogen cooled receiver at 0.5 torr. The two layers were separated, and the organic layer was dried over Na_2SO_4 at 10°, filtered, and redistilled, yielding 1.42 g (45%) of 1-methylcyclohexene-1-^{13}C boiling at 99-101° (reported[3] 110°). By refluxing the residue with iodine for a second two hour period and following the same work-up procedure an additional 0.45 g (14.2%) of product was isolated, giving a total yield of 1.87 g (59.2%). Nmr (chloroform-d): δ ca. 1.60 (m, 7H, ), 1.87 (m, 4H, ), ca. 5.26 (m, 1H, ). Satellites due to ^{13}C splitting were not observed due to peak overlap.

Toluene-1-^{13}C (90.00% ^{13}C). A 10 ml pear-shaped flask containing 1.82 g (0.019 mole) of 1-methylcyclohexene-1-^{13}C was attached to a 30 cm column that had been loosely packed with approximately 20 g of palladium/charcoal catalyst (30%) on top of a glass wool plug and preheated to 400° with a heating tape. The contents of the flask were introduced onto the column by heating the flask to 140-170° with an oil bath, and the distillate was condensed in a Dry Ice/2-ethoxyethanol cooled receiver. This procedure was repeated three more times, recharging the flask with the distillate after each run. Following the fourth pass, the column was evacuated (0.5 torr) for fifteen minutes to remove the residual product from the column. The final yield was 1.30 g (74.4%) of toluene-1-^{13}C. Nmr (chloroform-d): δ 2.27 (s/d, 3H, J = 5.4 Hz, CH_3-^{13}C), 7.0 (m, 5H, ring protons).

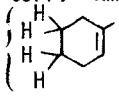
The aromatization reaction was monitored by ^{13}C nmr. A sample of 90% enriched toluene-1-^{13}C prepared in this manner showed C-1 only.

α-Bromotoluene-1-^{13}C (90.00% ^{13}C). A three-necked round bottom flask, fitted with a reflux condenser, gas trap, magnetic stirrer and addition funnel, was charged with 1.25 g (0.013 mole) of toluene-1-^{13}C in 25 ml of carbon tetrachloride. While stirring and irradiating the flask with a 200 Watt incandescent light, 2.15 g (0.013 mole) of bromine in 12.5 ml of carbon tetrachloride was added at such a rate that the color of the solution remained pink until the addition was completed. The flask was irradiated for an additional minute, and 20 ml of water was quickly added. The contents were separated in a separatory funnel and the organic layer was washed three times with 25 ml of water, dried ($CaCl_2$), and the carbon tetrachloride was evaporated. The liquid residue was vacuum distilled, yielding 1.49 g (64.3%) of α-bromotoluene-1-^{13}C, bp 52-56°, 0.5 torr (lit.[11] 114°, 15 torr). Nmr (chloroform-d): δ ca. 4.35 (s/d, 2H, J = 4 Hz, $BrCH_2$-^{13}C), 7.13 (m, 5H, ring protons).

Benzyl-1-^{13}C-diethylphosphonate (90.00% ^{13}C). Into a three-necked round bottom flask fitted with reflux condenser, drying tube ($CaCl_2$), magnetic stirrer, and addition funnel was placed 1.39 g (0.0085 mole) of triethyl phosphite. While stirring, 1.44 g (0.0084 mole) of α-bromotoluene-1-^{13}C was added dropwise over fifteen minutes. The flask was heated to 150° for one hour. The mixture was vacuum distilled, yielding 1.80 g (94.0%) of benzyl-1-^{13}C diethylphosphonate as a fraction boiling at 98-100°, 0.5 torr. Nmr (chloroform-d): δ 1.20 (t, 6H, J = 7 Hz, CH_3CH_2), 3.05 (d/d, 2H, J = 22 Hz/5.8 Hz, ^{13}C-CH_2P), ca. 3.9 (m, 4H, J = 7 Hz, $POCH_2CH_3$).

Sodium Acetate-2-^{13}C (91.92% ^{13}C). Following the procedure used for the preparation of sodium acetate-1-^{13}C 2.00 g (0.033 mole) of acetic-2-^{13}C acid (91.92% ^{13}C) was transformed into sodium acetate-2-^{13}C in a 100% yield (2.72 g).

Ethyl Acetate-2-^{13}C (91.92% ^{13}C). Using the procedure developed for the preparation of ethyl acetate-1-^{13}C, sodium acetate-2-^{13}C was esterified with 10 ml of triethylphosphate to yield 2.87 g (98.3%) of ethyl acetate-2-^{13}C. Nmr (chloroform-d): δ 1.20 (t, 3H, J = 7 Hz, CH_2CH_3), 1.98 (s/d, 3H, J = 124.0 Hz, $^{13}CH_3COO$), 4.02 (q, 2H, J = 7 Hz, CH_2CH_3).

1-Methyl-^{13}C-cyclohexene (91.92% ^{13}C). Following the procedure used for the preparation of 1-methylcyclohexene-1-^{13}C, 2.82 g (0.032 mole) of ethyl acetate-2-^{13}C, was allowed to react with the Grignard reagent grom 4.85 g (0.199 mole) of magnesium turnings and 21.8 g (0.095 mole) of 1,5-dibromopentane to yield 1.53 g (50%) of 1-methyl-^{13}C-cyclohexene after one reflux period. After a second work-up an additional 0.585 g (19.9%) was isolated, to give a total yield of 2.115 g (69.1%) of 1-methyl-^{13}C-cyclohexene, bp 98-101°, 0.5 torr. Nmr (chloroform-d): δ ca. 1.60 (m/d, 7H, J = 121.8 Hz, $^{13}\underline{CH_3}$-C and ), 1.87 (m, 4H, $\underline{CH_2}OC{=}C$), ca. 5.25 (m, 1H, CH_2-$\underline{CH}{=}C$).

Toluene-α-^{13}C (91.92% ^{13}C). Using the procedure for the preparation of toluene-1-^{13}C, 2.06 g (0.021 mole) of 1-methyl-^{13}C-cyclohexene was converted to 1.72 g (89%) of toluene-α-^{13}C following four passes and evacuation of the column. Gas chromatography and nmr showed the product to be greater than 99% pure. Nmr (chloroform-d): δ 2.30 (s/d, 3H, J = 123.0 Hz, $^{13}\underline{CH_3}C$), 7.02 (m, 5H, ring protons).

Benzoic-carbonyl-^{13}C Acid (91.92% ^{13}C). Into a 250 ml round bottom flask fitted with a magnetic stirrer and a reflux condenser was placed 1.68 g (0.018 mole) of toluene-α-^{13}C and 84 ml of distilled water. The mixture was heated to gentle reflux and 6.80 g (0.043 mole) of potassium permanganate was slowly added through the condenser over a half hour. The mixture was gently refluxed overnight, allowed to cool, and filtered. The colorless solution was reduced in volume to 10 ml and the solution was acidified. The white crystals were filtered, washed twice with cold water, and dried over $CaSO_4$ at 0.05 torr for six hours. The yield of benzoic-carboxyl-^{13}C acid was 1.11 g (50%) mp 123-124° (reported[11] 122.4°) after recrystallization from water. A second crop of crystals isolated from the mother liquor yielded 0.22 g (10%) of benzoic-carboxyl-^{13}C acid bringing the overall yield to 1.33 g (60%). Nmr (chloroform-d): δ 7.0-8.13 (m, 5H, ring protons), 11.80 (s, 1H, $COO\underline{H}$).

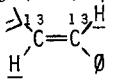
Benzoyl-carbonyl-^{13}C Chloride (91.92% ^{13}C). A mixture of 1.28 g (0.010 mole) of benzoic-carboxyl-^{13}C acid and 3.10 g (0.026 mole) of freshly distilled thionyl chloride was placed in a round bottom flask fitted with a reflux condenser and

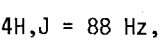
gas trap and was gently refluxed for two hours. The excess thionyl chloride was then removed by distillation and the liquid residue was vacuum distilled to yield 1.18 g (80%) of benzoyl-carbonyl-^{13}C chloride boiling at 38-40°, 0.55 torr (lit.[11] 71°, 9 torr). Nmr (chloroform-d): δ 7.35-8.10 (m, 5H, ring protons).

Lithium tri-t-butoxyaluminum Hydride (LTBA). Lithium tri-t-butoxyaluminum hydride was prepared according to the literature.[13]

Benzaldehyde-formyl-^{13}C (91.92% ^{13}C). A three-necked round bottom flask was fitted with an addition funnel, pentane thermometer, reflux condenser, drying tube ($CaCl_2$), and nitrogen inlet and outlet. Into this was placed 1.13 g (0.0080 mole) of benzoyl-carbonyl-^{13}C chloride dissolved in 15 ml of diglyme freshly distilled from $LiAlH_4$. While stirring, this mixture was cooled to -60°. A solution of 2.03 g (0.0080 mole) of LTBA in 10 ml of diglyme was added dropwise at such a rate that the temperature variation in the reaction flask was not more than 2°. The mixture was allowed to warm to room temperature over an hour, and was poured onto ice, filtered, and transferred to a separatory funnel. The aqueous layer was extracted three times with 25 ml portions of ether, which were combined, washed three times with water, dried (Na_2SO_4), and the solvent was evaporated. The residue was vacuum distilled, yielding a fraction boiling at 27.28°, 0.2 torr (reported[6] 63.4°, 13 torr). When gas chromatography showed two peaks the fraction was treated with a saturated sodium bisulfite solution, filtered, and the solid was treated with sodium bicarbonate until the solid dissolved. Extraction with ether, followed by removal of the solvent and redistillation, yielded 0.509 g (59.5%) of benzaldehyde-carbonyl-^{13}C. Nmr (chloroform-d): δ 7.2-7.85 (m, 5H, ring protons), 9.85 (s/d, 1H, J = 169.0 Hz, ^{13}CHO).

1-Phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C (trans-stilbene)(82.74% di-^{13}C). A three-necked round bottom flask was fitted with a thermometer, drying tube ($CaCl_2$), addition funnel, an magnetic stirrer and 0.285 g (0.0052 mole) of sodium methoxide was added, followed by 1.005 g (0.0046 mole) of benzyl-1-^{13}C diethylphosphonate in 5 ml of dimethylformamide. The solution was stirred until thermal equilibrium was reached, and then 0.468 g (0.0044 mole) of benzaldehyde-formyl-

^{13}C in 5 ml of dimethylformamide was added dropwise. The temperature was kept between 30° and 40° by stirring and cooling over ice when necessary. Following completion of the addition the solution was allowed to cool to room temperature, and the contents were poured onto ice. The white crystals of 1-phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C were filtered, washed twice with water, and dried in a desiccator overnight. The yield following recrystallization from ethanol was 0.8374 g (60%) mp 127-8° (lit[11] 124°). Nmr (chloroform-d): δ 6.89 (s/d, 2H, J = 132 Hz  , 6.98-7.48 (m, 10H, ring protons).

1-Phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C (9.53% di-^{13}C). A solution of 48.1 mg (0.266 mmole) of 1-phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C in 25 ml of anhydrous ether and 0.02 g (0.088 mmole) of platinum oxide were placed in a 250 ml pressure bottle which was attached to a Parr hydrogenator and shaken under ca. 45 psi of hydrogen for one-half hour. The solution was filtered and the solvent was removed by evaporation. The crystals were recrystallized from methanol to yield 0.0414 g (85%) of 1-phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C, mp 56-56.5° (lit.[11] 52.2°). Nmr (chloroform-d): δ 3.56 (s/d,4H,J = 88 Hz, ), 7.07 (m,10H, ring protons). Other ^{13}C splittings were unobservable due to peak overlap.

2-Phenyl-3-phenyl-1-^{13}C-oxirane-2-^{13}C (9.53% di-^{13}C). Into a 10 ml round bottom flask fitted with a reflux condenser and magnetic stirrer was placed 23.0 mg (0.127 mmole) of 1-phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C, 24.1 mg (0.140 mmole) of m-chloroperoxybenzoic acid, and 6 ml of benzene. The m-chloroperbenzoic acid had been washed with a phosphate buffer at pH 7.5 to remove m-chlorobenzoic acid prior to use. The mixture was stirred for 72 hours while maintaining the temperature at 35°. The solvent was evaporated, leaving a white crystalline compound whose mp of 69-78° showed it to be impure 2-phenyl-3-phenyl-1-^{13}C-oxirane-2-^{13}C. Following purification by preparative thin layer chromatography (silica gel GF 254, carbon tetrachloride) crystals melting at 76-77° (lit.[12] 68-69°) were obtained. Yield: 12.2 mg (44.3%). M.S.: m/e (%) 167 (100), 90 (96), 89 (85), 196 (84), 47 (45), 51 (40).

meso-1,2-Dibromo-1-phenyl-2-phenyl-1-^{13}C-ethane-1-^{13}C (9.53% di-^{13}C). To a solution of 45.6 mg (25.0 mmole) of 1-phenyl-2-phenyl-1-^{13}C-ethene-1-^{13}C in anhydrous ether was added 48.0 mg (30.0 mmole) of bromine while stirring. The mixture was stirred for one hour and poured onto a Hirsch funnel. The crystals were washed with ether until white, yielding 59.7 mg (69.4%) of meso-1,2-dibromo-1-phenyl-2-phenyl-1-^{13}C, mp 218-220° (lit.[10] 235-237°). M.S.: m/e (%) 180 (100), 179 (38), 259 (32), 261 (31), 89 (31), 77 (20).

1-Phenyl-2-phenyl-1-^{13}C-ethyne-1-^{13}C (9.53% di-^{13}C). To a solution of 76 mg (13.5 mmole) of potassium hydroxide in 2 ml of absolute ethanol, heated to just below reflux, was added 59.65 mg (0.175 mmole) of meso-1,2-dibromo-1-phenyl-2-phenyl-1-^{13}C-ethane. The mixture was refluxed for 24 hours, the solvent removed, and the product was recrystallized from ethanol to yield 20.8 mg (65%) of 1-phenyl-2-phenyl-1-^{13}C-ethyne with a mp of 63.3-64.5° (lit.[10] 63.5°). Nmr (chloroform-d) δ 7.2 (m, 10H, ring protons). Sp'itting by the ^{13}C's was not observed due to the width of the multiplet peaks.

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