Journal of Labelled Compounds — January-March — Vol. IV, No. 1

Synthesis of ^{14}C-Labeled Olefins using the Wittig Reaction

M. A. MUHS
Shell Development Company, Emeryville, California 94608

Received on August 1st, 1967

SUMMARY

*The Wittig synthesis has been used to prepare conveniently carbon-*14 *labeled* 1*-olefins in the* C_5 *to* C_8 *range in about* 60 % *yield. The chemical and radiochemical purities of the products exceeded* 99.5 %. *The common source of carbon-*14 *in these reactions was methyl-*^{14}C*-triphenylphosphonium iodide which was readily and quantitatively prepared from commercially available methyl-*^{14}C *iodide.*

INTRODUCTION

We have had a continuing demand for ^{14}C-labeled 1-olefins in our laboratories. In the course of this work we have been unable to obtain labeled olefins from commercial suppliers with satisfactory radiochemical purity. For example, the radiochemical purities, as determined by gas-liquid radiochromatography (GLRC) (1), of some commercial products are listed in Table 1.

TABLE 1. Radiochemical purities of commercial labeled olefins

Compound	Radiochemical Purity, %
Cyclohexene-1-^{14}C	88
1-Dodecene-1-^{14}C	< 0.1
1-Tetradecene-1-^{14}C (A)	< 0.1
1-Tetradecene-1-^{14}C (B)	40

The 1-tetradecene-1-^{14}C (B) was what the supplier delivered after he had been notified of the poor quality of his original product (A).

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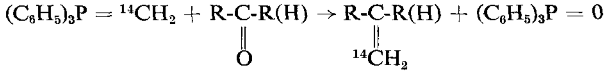
* See bibliography.

Because of this difficulty we were faced with either purchasing and purifying impure materials or synthesizing the labeled olefins. The former appeared to be a poor choice since the commercial products often contained little or none of the desired labeled material. The second choice was more favorable since the Wittig reaction (2) as modified by Corey and coworkers (3, 4) offered a simple, convenient technique for the synthesis of radiochemically pure, uniquely labeled 1-olefins from a convenient source of carbon-14. In this reaction :



$$(C_6H_5)_3P = {}^{14}CH_2 + \underset{\substack{\| \\ O}}{R\text{-}C\text{-}R(H)} \rightarrow \underset{\substack{\| \\ {}^{14}CH_2}}{R\text{-}C\text{-}R(H)} + (C_6H_5)_3P = O$$

the labeled methylenephosphorane intermediate can be prepared from the readily available methyl-^{14}C iodide. The reaction proceeds without rearrangement of the carbon skeleton or the double bond.

This technique was used previously to prepare propylene-1-^{14}C, 1-butene-1-^{14}C and 5-methylene-^{14}C-bicyclo[2.2.1] hept-2-ene (5). There have been no other reports on the use of this technique for the preparation of simple aliphatic 1-olefins. This report describes such an application to the syntheses of ^{14}C-labeled olefins in the C_5 to C_8 range.

RESULTS AND DISCUSSION.

The methyl-^{14}C-triphenylphosphonium halide, which was used for the introduction of carbon-14 into the olefins, was prepared by the reaction of a methyl-^{14}C halide (bromide or iodide) with triphenyl phosphine. The preparation of either salt is simple and essentially quantitative. The cost of the methyl-^{14}C iodide is about one-half of that of the bromide, but Collins and

TABLE 2. Summary of the Wittig olefin syntheses

Olefin	Carbonyl	Yield, %		Purities, % (a)		Activity, μC
		Iodide	Bromide	Chemical	Radio-chem.	
1-Pentene	*n*-Butyraldehyde	58	61	99.9	99.9	470
2-Methyl-1-pentene	2-Pentanone	64	71	99.9	—	—
4-Methyl-1-pentene	iso-Valeraldehyde	66	72	99.9	99.9	282
1-Hexene	*n*-Valeraldehyde	57	49	99.8	99.6	449
1-Heptene	*n*-Hexaldehyde	65	72	99.8	99.6	284
Methylenecyclohexane	Cyclohexanone	66	75	99.8	—	—
1-Octene	*n*-Heptaldehyde	54	56	99.3	99.9	218

(a) Prepared from the iodide salt.

Hammond (6) reported difficulty in the synthesis of methylenecyclopentane using methyltriphenylphosphonium iodide, while the reaction went satisfactorily with the bromide. In this work a series of seven olefins in the C_5 to C_8 range was prepared using each of the salts. The yields are shown in Table 2. Both salts gave satisfactory yields with the bromide salt being slightly better (yields higher by 6 % relative). Since this was only a minor increase and because of the cost factor, the ^{14}C-labeled iodide salt was selected for the synthesis of the ^{14}C-labeled olefins. This salt can be stored and used when necessary.

The optimum ratio of reactants was established from a series of experiments involving the synthesis of 1-heptene. These results are shown in Table 3. Equimolar amounts of the phosphonium iodide, the aldehyde, and the base gave the highest yields. The self-condensation of aldehydes in the presence of base is always a possible side reaction in this synthesis, and the presence of excess base drastically lowered the yield of product. Having excess aldehyde present did not help this situation since this caused a slight reduction in yield relative to the equimolar case. Finally it is seen that the base takes a direct part in the Wittig reaction, since using half an equivalent reduced the yield by one-half in comparison with the equimolar case.

TABLE 3. Effect of varying amounts of reactants on yield of 1-heptene

Reactants, Molar Ratio			
$\varnothing_3PCH_3I$	*n*-Hexaldehyde	Base	Yield, %
1	1	1	65
1	2	1	57
1	1	2	19
1	1	1/2	33

Although Corey *et al* (3, 4) in the original work on this technique did not mention the formation of benzene as a side product, this was observed by Atkinson and coworkers (5); and in this work, unlabeled benzene was formed to the extent of 15 to 25 % of the crude reaction product. A possible path for the formation of benzene has been given by Seyferth, Heeren and Hughes (7). The benzene side product and traces of unreacted carbonyl compound that distilled with the olefin were readily separated from the olefin using preparative scale gas chromatography.

The experimental procedure (details appear in the Experimental Section) has been designed to minimize handling losses and is most convenient for use in the 8 to 10 millimole range. The synthesis is simple to run and the complete preparation (synthesis and purification) can be done in three hours.

A summary of the olefins prepared by this technique is given in Table 2. Included in this table are the yields of 1-olefins, the chemical and radiochemical purities of the purified products (as determined by gas-liquid radiochromatography) (1) and the activities of the labeled compounds prepared. The yields, while not spectacular, are satisfactory for this one-step reaction sequence. It should be pointed out that these are rigorous yield values, determined from the amount of isolated purified olefin.

A comparison of the technique described in this paper with other techniques using the Wittig reaction for the synthesis of methylenecyclohexane is presented in Table 4.

TABLE 4. Yields of methylenecyclohexane

Technique	Yield, %	Ref
Conventional Wittig Reaction	35-40	8
Corey Modification		
Corey et al	86	4
Atkinson et al	50	5
This Work	75	—

The yield obtained in this work is superior to that reported previously with the exception of that reported by Corey and coworkers (4). They did not mention the formation of benzene and simply based the yield on the material that distilled from the reaction mixture. Therefore, their value may be high.

Table 2 shows that simple aliphatic 1-olefins in the C_5 to C_8 range can be prepared in about 60 % yield. The only other simple aliphatic 1- olefins that have been prepared by this technique are ethylene, propylene, and 1-butene. These were prepared in 40, 46 and 50 % yields, respectively ,by Atkinson and coworkers (5).

In our syntheses, the radiochemical and chemical yields agreed. The final activity was distributed between the olefin product and the reaction residue. This accounted for over 90 % of the initial activity of the methyl-^{14}C-triphenylphosphonium iodide.

While Atkinson and coworkers (5) were the first to prepare chemically pure ^{14}C-labeled 1-olefins using the Wittig reaction, they did not determine the radiochemical purity of their products. In this work we have established that preparative scale gas chromatography is a convenient technique for the separation of the labeled 1-olefin from side products; and, as is seen in Table 2, the products had excellent chemical and radiochemical purities.

The potentiality of the Wittig reaction for the synthesis of ^{14}C-labeled olefins, first used by Atkinson and coworkers (5), has been further realized in this work. The technique is a simple, convenient one that has been shown to work from ethylene through the octenes; and with suitable modification of the work-up procedure, it should be possible to extend it to the synthesis of higher olefins. This reaction is particularly useful since a great variety of labeled olefins can be prepared in one step from a convenient, stable source of carbon-14, the phosphonium salt. Finally, it should be emphasized that the product produced is labeled at a unique position and that the double bond formed is also in a unique position.

EXPERIMENTAL

Purification of Dimethyl Sulfoxide

Into a 3000 ml round-bottomed flask, equipped with a drying tube, were placed 2000 ml of dimethyl sulfoxide (Mallinckrodt Analytical Reagent) and 20 g of calcium hydride. The mixture was allowed to stand 24 hours at room temperature and then distilled under nitrogen at reduced pressure. The first 150 ml was discarded and then about 1500 ml (bp 83°/22 mm) was collected. The purified material was stored under nitrogen in serum-stoppered bottles.

Methyl-^{14}C- triphenylphosphonium Iodide[9])

Into a 50 ml bottle were placed 14.33 g of triphenylphosphine (54.6 mmoles, Matheson, Coleman, and Bell) and 17 ml of anhydrous benzene. Solution was effected in about 10 minutes at room temperature. To this was added 7.76 g of methyl-^{14}C iodide (54.7 mmoles, 9.22 mc, chemical and radiochemical purity as determined by GLRC were greater than 99 %, material obtained from New England Nuclear Corporation) in 6 ml of anhydrous benzene and the bottle was stoppered with a serum cap. An immediate precipitate formed; and during the first 10 minutes, the reaction mixture was cooled in a stream of water. The mixture was allowed to stand overnight at room temperature, and the white solid was isolated by filtration and washed thoroughly with benzene. Drying at 100° and 0.05 mm for four hours gave 21.20 g of methyl-^{14}C-triphenylphosphonium iodide (8.85 mc, 0.417 mc/g, 96 % yield).

Methyltriphenylphosphonium Bromide

The method of Wittig and Schoellkopf(8) was followed to give the bromide in 99 % yield.

Carbonyl Compounds

Commercially available materials were purified by distillation and preparative scale gas chromatography. Final products had purities better than 99 % as determined by gas chromatography and infrared spectra identical with those of authentic materials.

Sodium Hydride-Dimethyl Sulfoxide Solution

Into a 100 ml three-necked round-bottomed flask, equipped with a magnetic stirrer, an one-way stop-cock and two serum caps was placed 4.70 g of a 52.6 % suspension of sodium hydride in mineral oil (2.47 g sodium hydride, 103 mmoles, Metal Hydrides Inc.). The system was alternately evacuated and filled with nitrogen six times so that it contained a nitrogen atmosphere. With nitrogen flowing into the system, the stop-cock was opened; 55 ml of distilled, dry dimethyl sulfoxide was introduced; and the stop-cock was connected to a drying tube. The stirred mixture was heated for 150 minutes in a 70° bath. After this time hydrogen evolution had stopped, and a grey suspension resulted. Nitrogen flow was stopped, the stop-cock closed, and its open end sealed with a serum stopper. When needed, the basic solution was removed with a 5 ml hypodermic syringe by passing its needle through the open stop-cock into the solution. Having the system under a slight pressure of nitrogen, facilitated sampling. Titration of an aliquot of the basic solution with acid indicated a normality of about 1.9.

Olefin Synthesis — General Procedure

The apparatus used consisted of a 50 ml, three-necked round-bottomed flask with magnetic stirrer, a distilling head, and a 20 ml spiral trap (Cf. traps Fig. 1). The flask and distilling head were sealed with serum stoppers, and the outlet of the trap was connected to a three-way stop-cock.

Methyl-^{14}C-triphenylphosphonium iodide (3.23 g, 8.0 mmoles) was added to the flask, which contained a nitrogen atmosphere and was protected

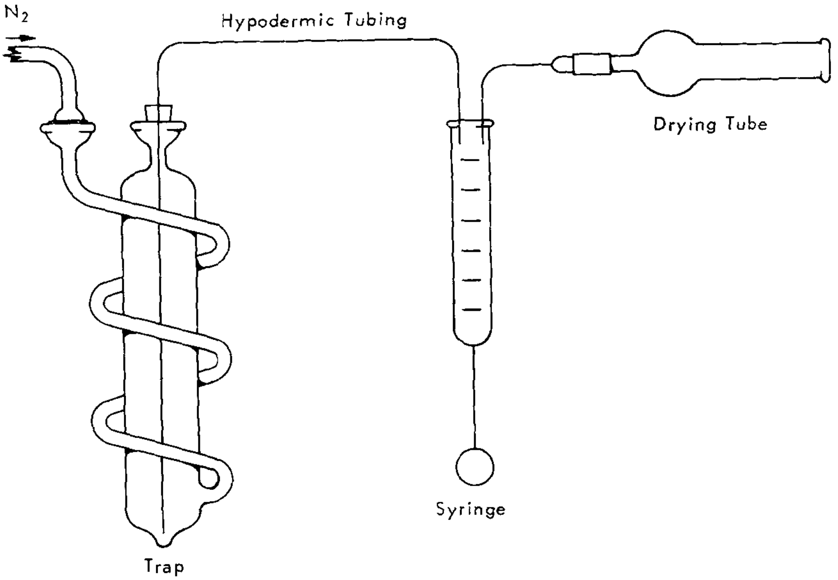


Fig. 1. — Wittig reaction transfer apparatus

from moisture by a drying tube. Using a syringe, 10 ml of purified dimethyl sulfoxide was added to the reaction flask; and the salt quickly dissolved with the aid of mild heating (70° bath). The solution was cooled in an ice bath; and with a syringe, the sodium hydride-dimethyl sulfoxide solution was added (8.4 mmoles, generally 4-5 ml). The mixture was allowed to warm to room temperature and was stirred for 10 minutes. After cooling the trap in liquid nitrogen, the carbonyl compound (8.0 mmoles) was added via a syringe; and the mixture was stirred for 30 minutes. The reaction mixture was cooled in ice, and the serum cap on the distilling head was replaced by a capillary extending into the reaction mixture. The ice bath was removed, and the product was distilled into the trap by applying a vacuum (22 mm). Distillation was carried out for 10 minutes at room temperature and for 5-10 minutes (depending on product volatility), at 70°. The trap was removed, allowed to warm to ice temperature, and sealed with serum stoppers.

The material in the trap (about 0.8 ml) consisting of olefin, benzene, and a trace of unreacted carbonyl was transferred to a 1.0 ml Hamilton syringe (1001-N) as is illustrated in Figure 1. The hypodermic tubing (20 gauge) was passed through the serum stopper at the trap entrance to the bottom of the trap. The other end of the tubing passed through the serum stopper in the 1.0 ml syringe. The syringe needle was closed with a rubber septum, and a hypodermic needle connected to a drying tube was put through the serum stopper on the syringe. The syringe was cooled in dry ice-acetone, and the sample was transferred from the trap to the syringe by the application of slight nitrogen pressure at the trap outlet. The transfer tubing was removed from the syringe, and the syringe was allowed to warm to room temperature (to insure tight fit of the plunger). The vent needle was removed when the temperature was about 0°. The serum stopper was replaced with the gas-tight syringe plunger; the syringe was inverted; the septum, removed; and the sample was injected into the preparative scale gas chromatography apparatus.

Preparative Scale Gas Chromatography

A Wilken's Autoprep A-700 was used for the preparative scale gas chromatography. The injection port, the detector, and the collecter were heated to 200°. Helium was used as the carrier gas at 100 ml/min, and the products were trapped in 20 ml spiral traps cooled in liquid nitrogen.

The aldehydes were purified on a 10′ × 3/8″ 30 % Carbowax-20M-terephthalic acid column with a sample size of 1 ml. The following column temperatures were used : isobutyraldehyde, 65°; n-butyraldehyde, 76°; isovaleraldehyde, 95°; valeraldehyde, 100°; n-hexaldehyde, 126°; n-heptaldehyde, 150°. Cyclohexanone and 2-pentanone were satisfactorily purified by distillation alone.

The distilled reaction products were purified on a 20′ × 3/8″ 30 % 1,2,3-tris(2-cyanoethoxy) propane column. In all cases, the olefin emerged before the benzene (15-25 % of distilled product) and traces of unreacted carbonyl compounds. The following column temperatures were used : 1-pentene, 50°; 4-methyl-1-pentene, 80°; 1-hexene, 80°; 1-heptene, 85°; 1-octene, 85°; 2-methyl-1-pentene, 90°; methylenecyclohexane, 91°. With the 1-pentene, after the emergence of the olefin, the column was programmed to 100° to speed up removal of benzene. All others were run isothermally.

GLRC Conditions

The combination of gas chromatographic apparatus and ion chamber described previously (1) was used for this analysis. All olefins were analyzed on two different columns. All but two were studied on a 12′ × 1/4″ Hallcomid M-18 (N, N-dimethylamide of stearic acid) column at temperatures of 85-95° depending on the olefin, and on a 6′ × 1/4″ column containing 39.6 % of a 4.18 M silver nitrate-ethylene glycol solution at 40°. The 1-pentene-1-^{14}C and the 2-methyl-1-pentene were analyzed on a 12′ × 1/4″ 20 % SF-96 column at 35° and on a 12′ × 1/4″ column containing 35.5 % of a 5.37 M silver nitrate-ethylene glycol solution. The chemical and radiochemical purities obtained are listed in Table 2.

Liquid Scintillation Counting

A Packard Tri-Carb automatic liquid scintillation counter Model 3314 was used. The material to be counted was placed in a counting vial with 20 ml of counting solution (6 g 2,5-diphenyloxazole and 0.1 g 1,4-di-[2-(4-methyl-5-phenyloxazoyl)]-benzene diluted to one liter with toluene). It was assumed that no quenching occurred with the 1-4 μl samples used.

BIBLIOGRAPHY

1. Muhs, M. A., Bastin, E. L. and Gordon, B. E. — *Int. J. Appl. Rad. Isotopes*, **16** : 537 (1965).
2. Maercker, A. " Organic Reactions ", Adams Roger, ed., John Willey and Sons, Inc., New York, 1965, Vol. 14, pp. 270-490.
3. Corey, E. J. and Chaykovsky, M. — *J. Am. Chem. Soc.*, **84** : 866 (1962).
4. Greenwald, R., Chaykovsky, M. and Corey, E. J. — *J. Org. Chem.*, **28** : 1128 (1963).
5. Atkinson, J. G. Fisher, M. H., Horley, D., Morse, A. T., Stuart, R. S. and Synnes, S. — *Can. J. Chem.*, **43** : 1614 (1965).
6. Collins, C. H. and Hammond, G. S. — *J. Org. Chem.*, **25** : 1434 (1960).
7. Seyferth, D., Heeren, J. K. and Hughes, W. B. Jr. — *J. Am. Chem. Soc.*, **84**: 1764(1962).
8. Wittig, G. and Schoellkopf, U. — " Organic Syntheses ", M. S. Newman, ed., John Wiley and Sons, Inc., New Tork, 1960, Vol. 40, p. 66.
9. Michaelis, A. and Soden, H. V. — *Ann.*, **229** : 310 (1885).