THE SYNTHESES OF 1,1,1—TRIFLUORO—2—SUBSTITUTED—PHENYL—2—PROPYL—3—^{14}C *P*—TOLUENESULFONATES*

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ABSTRACT

1,1,1,- Trifluoro- 2- substituted- phenyl- 2- propanols- 3- ^{14}C were prepared from addition of methyl- ^{14}C magnesium iodide to appropriate trifluoroacetophenone. These alcohols were converted into tosylates by reaction with *n* – butyllithium and then with *p*- toluenesulfonyl chloride. The yield, boiling point or melting point and pertinent spectral data of these compounds are reported.

Keywords: 1,1,1- Trifluoro- 2- substituted- phenyl- 2- propanols- 3- ^{14}C 1,1,1- Trifluoro- 2- substituted- phenyl- 2- propyl - 3- ^{14}C *p*- toluenesulfonates Trifluoroacetophenones ^{14}C- Labelled compound

I . INTRODUCTION

For a number of years Dr. Fry's research group has been investigating the mechanisms of substitution and elimination reactions using the successive labelling isotope effect technique. In particular, we have sought a convenient "calibration example" for the E1 mechanism. We have been led to a carbon- 14 isotope effect study of beta- labeled 1,1,1- trifluoro- 2- substituted- phenyl- 2- propyl tosylates by the reports[1,2] that these compounds solvolyze in a variety of solvents by the SN1/E1 mechanism. No radiolabeled version of these compounds were available commercially, so we undertook the syntheses described in this paper. 1,1,1- trifluoro- 2- substituted- phenyl- 2- propyl- 3- ^{14}C *p*- toluenesulfonates were synthesized from the alcohols by treatment with butyl lithium followed by tosyl chloride[2]. The labeled alcohols were prepared by Grignard reactions using the trifluoroacetophenones and commercially available carbon- 14 labeled methyl iodide. The trifluoroacetophenones were obtained by the reactions between the corresponding substituted- phenylmagnesium bromides and trifluoroacetic acid[3]. The scheme in Fig.1 outlines the synthesis process. In each case, the radiochemical yield and the chemical yield were the same. The specific activities of the products were 88 MBq/mol and were diluted using inactive carrier to 12 MBq/mol which was suitable for measuring thecarbon- 14 kinetic isotope effects. In order to demonstrate their purities, the tosylate products were recrystallized three times. It was found that the molar activities for the first,

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second and third recrystallization were constant. The solvolysis reaction of the unsubstituted compound was carried out in glacial acetic acid at 75°C. The ester produced after 100% solvolysis reaction was reduced to alcohol by using $LiAlH_4$ and then the alcohol was converted to tosylate. The specific activity measured from the neat starting material was 13.9316 MBq/mol ± 0.0455 (standard deviation) and the specific activity determined from the derivative of the product after 100% reaction was 13.9305 MBq/mol ± 0.0274. The good agreement of the values gave us confidence that the chemical and the radiochemical purity of the prepared tosylate were very good. For the *p*- chloro and the *p*- methyl compound, the results were almost the same.

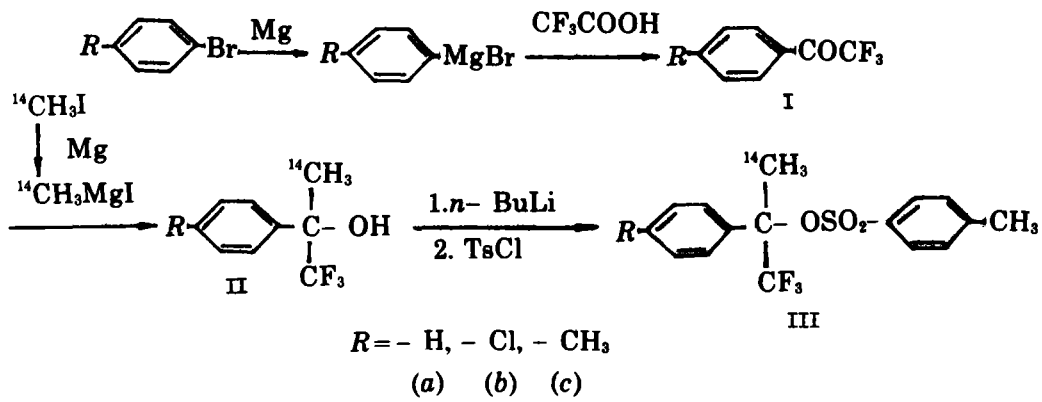

Fig.1 The syntheses process of 1,1,1—trifluoro—2—substituted—phenyl—2—propyl—3—^{14}C *p*—toluenesulfonates

II. EXPERIMENTAL

2,2,2—Trifluoroacetophenones(I)

2,2,2- Trifluoroacetophenones were synthesized from trifluoroacetic acid and 3 moles of the appropriate arylmagnesium bromide in a similar manner to that reported by E.D.Bergmann et al[3]. The arylmagnesium bromide was made by slow addition of 1 mol aryl bromide (bromobenzene, *p*- bromochlorobenzene and *p*- bromotoluene respectively) to an equivalent amount of magnesium turnings in 300 ml of dried ethyl ether. Almost all the magnesium was dissolved after the mixture was stirred at room temperature for two hours. A solution of 38 g of trifluoroacetic acid (0.33mol) in 100ml of anhydrous ether was added dropwise to a stirred solution of the Grignard reagent at ice- bath temperature. After one more hour at 0°C and 15 min at the boiling temperature of ether, the reaction product was decomposed with 5% H_2SO_4 and the aqueous layer extracted twice with ether. The combined extracts were dried over anhydrous Na_2SO_4. After removing all the ether solvent, the reaction mixture was distilled and gave desired ketone. The ^1H NMR spectrum of the product showed it was the same as that of the authentic 2,2,2- trifluoroacetophenone. The yield, boiling point of these ketones are showed in Table 1.

Table 1

The yield, boiling point of the ketones

Ketones	Yield	b.p.(°C)	b.p.in Ref.[3](°C)
2,2,2- Trifluoroacetophenone (I_a)	68%	160	165
4- chloro- ω,ω,ω- Trifluoroacetophenone (I_b)	70%	60- 65(3.5 mm)	92- 93(12 mm)
4- methyl- ω,ω,ω- Trifluoroacetophenone (I_c)	68.5%	50- 55(3.5 mm)	85- 86(18 mm)

1,1,1-Trifluoro-2-substituted-phenyl-2-propanols-3-^{14}C (II)

The alcohols were obtained by the addition of methyl- ^{14}C- magnesium iodide to appropriate trifluoroacetophenone following the general procedure. The methyl- magnesium iodide- ^{14}C was made by solw addition of 30 g methyl iodide- ^{14}C (0.21mol, 18.5MBq) to an equivalent amount of magnesium turnings in 80ml of dried diethyl ether. Almost all the magnesium was dissolved after the mixture has been stirred in the ice bath for one hour. A solution of substituted trifluoroacetophenone (0.2mol) in 75ml of dried ether was added dropwise to the stirred solution of the Grignard reagent at 0°C. The stirring was continued at room temperature overnight. It was then hydrolyzed with 25ml of an ice- chilled saturated solution of ammonium chloride. The mixture was filtered and the inorganic residue was washed twice with 50ml of ether. The combined ether solution was dried over anhydrous sodium sulfate and decolorized with carbon powder. Finally the alcohol product was isolated by distillation. In each case, the radiochemical yield determined by liquid scintillation counting of a diluted sample was the same as the chemical yield. The yield, boiling point and pertinent ^{1}H NMR spectral data of these compounds are listed as follows.

1,1,1- Trifluoro- 2- phenyl- 2- propanol- 3- ^{14}C(II_a):

Yield 90%; b.p.58- 61°C (3.5 Torr) (Ref. [4]62- 66°C (4.5 Torr)); ^{1}H NMR ($CDCl_3$) δ 1.70(S,3,CF_3CCH_3), 2.45 (S,1,OH), 7.20- 7.50 (m, 5, C_6H_5)

1,1,1- Trifluoro- 2- (4- Chlorophenyl)- 2- propanol- 3- ^{14}C(II_b):

Yield 87%; b.p.80°C (2.5mm) (Ref. [2]80°C (2.4 Torr)); ^{1}H NMR ($CDCl_3$) δ 1.70(S,3,CF_3CCH_3), 2.80 (S,1, OH), 7.20 and 7.30 (A_2B_2, 4, J=7.5Hz, C_6H_4)

1,1,1- Trifluoro- 2- (4- methylphenyl)- 2- propanol- 3- ^{14}C(II_c):

Yield 88%; b.p.80- 83°C (2.5mm) (Ref. [2]51°C (0.7 Torr)); ^{1}H NMR ($CDCl_3$) δ 1.70(S,3,CF_3CCH_3), 2.30 (S,3,$ArCH_3$), 2.80 (S,1, OH), 7.05 and 7.30 (A_2B_2, 4, J=7.5Hz, C_6H_4

1,1,1-Trifluoro-2-substituted-phenyl-2-propyl-3-^{14}C *p*-toluenesulfonates(III)

A 500ml three- necked flask fitted with a septum stopper, a condenser with drying tube, and a pressure- equalizing dropping funnel with nitrogen- inlet tube, was dried under nitrogen. To this, 1,1,1- trifluoro- 2- substituted- phenyl- 2- propanol- 3- ^{14}C (70- 180mmol) in 100ml of tetrahydrofuran was added. *n*- Butyllithium in hexanes, 54ml- 135ml (ca. 85- 200mmol), was added dropwise using a syringe at 0°C with magnetic stirring. This mixture was allowed to stir for 0.5 h and was then cooled

to - 40°C. Tosyl chloride (70- 180mmol) in 100ml THF was added and the solution was then allowed to warm to room temperature. The solution was stirred for 6 h (for the *p*- methyl compound) and overnight (for the unsubstituted compound and the *p*- chloro compound). The solvent was stripped off. The residue was extracted with ethyl ether and the ethereal solution was washed with 200ml of ice- chilled 5% sodium bicarbonate solution. It was dried (Na_2SO_4) and evaporated. The residue was recrystallized from benzene- hexane (1:4). The specific activity of the white crystal product was 88.1 MBq/mol. Both the chemical yield and the radiochemical yield were the same. The yield based on the alcohol, melting point, proton NMR spectral data for the three tosylates prepared are summarized as follows:

1,1,1- Trifluoro- 2- phenyl- 2- propyl- 3- ^{14}C *p*- toluenesulfonate (Ⅲ$_a$):

Yield 50%; mp 101- 102°C (Ref.[2] 103.5°C); ^1H NMR ($CDCl_3$) δ 2.13 (S,3, CF_3CCH_3), 2.35 (S,3, $ArCH_3$), 7.13 and 7.58 (A_2B_2, 4, J=8.0Hz, MeC_6H_4), 7.25- 7.35 (m,5,C_6H_5)

1,1,1- Trifluoro- 2- (4- chlorophenyl)- 2- propyl- 3- ^{14}C p- toluenesulfonate (Ⅲ$_b$):

Yield 55%; mp 91- 92°C (Ref.[2]93- 93.5°C); ^1H NMR ($CDCl_3$) δ 2.13 (S,3,CF_3CCH_3), 2.37 (S,3,$ArCH_3$), 7.13 and 7.58 (A_2B_2, 4, J=8.3Hz, MeC_6H_4), 7.23 (should be A_2B_2 but can't be separated, 4,ClC_6H_4)

1,1,1- Trifluoro- 2- (4- methylphenyl)- 2- propyl- 3- ^{14}C *p*- toluenesulfonate (Ⅲ$_c$):

Yield 46%; mp 67- 68°C (Ref.[2] 73°C); ^1H NMR ($CDCl_3$)δ 2.11 (S,3,CF_3CCH_3), 2.26 (S,3,$ArCH_3$), 2.33 (S,3,$ArCH_3$), 7.05 and 7.25 (A_2B_2, 4, J=7.5Hz, C_6H_4), 7.13 and 7.58 (A_2B_2, 4, J=8.0Hz, $MeC_6H_4SO_3$)

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