Monitoring Atom Transfer Radical Polymerisation using ^{14}C-Radiolabelled Initiators

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Supporting Information

Synthetic Procedures

A) Synthesis of Benzyl 2-bromo isobutyrate

To a 250ml one neck round bottomed flask containing a magnetic stirrer flushed with nitrogen was added dry dichloromethane (150ml), benzyl alchohol (0.1 mol), triethylamine (1.1eq) and dimethyl amino pyridine (0.013eq). The reaction mixture was cooled to 0^0C using an ice water bath. With stirring, bromo isobutyryl bromide (1.1eq) was added dropwise to the reaction mixture using a pressure equalizing dropping funnel. Once this addition was complete, the reaction flask was left to stir for twenty four hours initially at 0^0C but allowed to warm to room temperature.
The reaction mixture was evaporated to remove the solvent to yield a crude yellow oil and a cream precipitate. Dilute hydrochloric acid and diethyl ether were added and the product was washed 4 times. Finally the mixture was washed with dilute sodium carbonate The combined diethyl ether layers were dried over sodium sulphate, filtered and evaporated to yield a bronze coloured oil product.The structure and purity of the final product was confirm by ^{1}H NMR, ^{13}C NMR and Mass Spectrometery. Chemical purity > 95%. Chemical Yield 23.9g (93%).

Figure S1: ^{1}H NMR spectrum of Benzyl 2-bromo isobutyrate

Figure S2: ^{13}C NMR spectrum of Benzyl 2-bromo isobutyrate

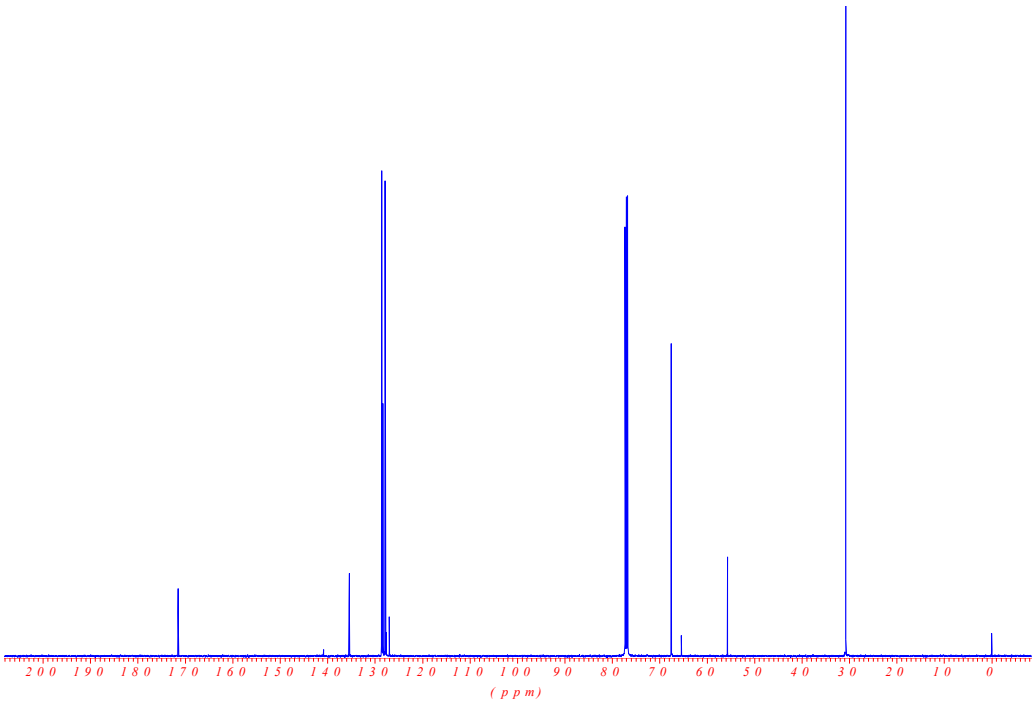
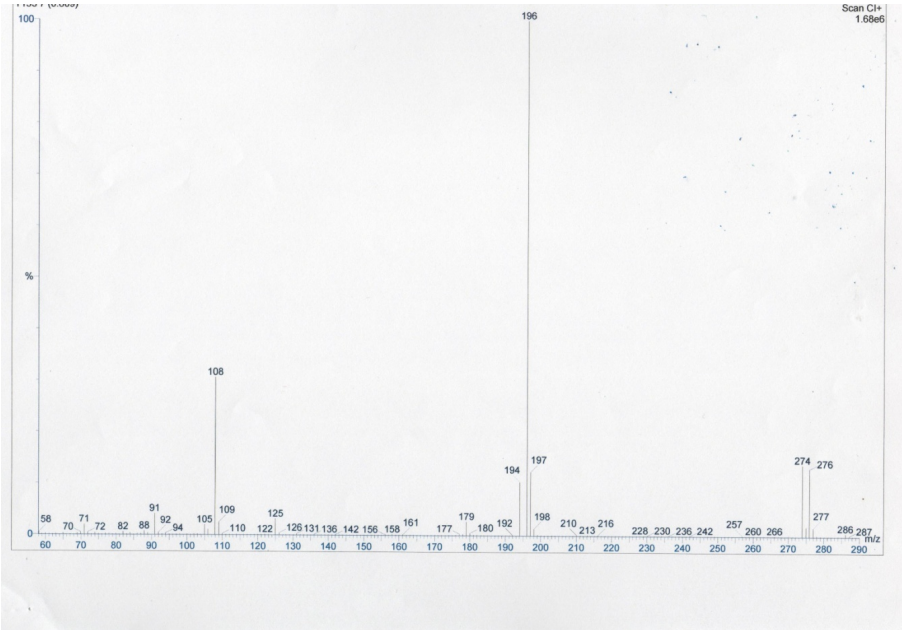


Figure S3: Mass Spectrum of Benzyl 2-bromo isobutyrate



Theoretical Mass = 274 Daltons

B) Synthesis of 3

The synthesis of 3 utlised benzyl ($^{14}CH_2$) alcohol (0.0203 moles, 13.56mCi) and followed the procedure described above. The radiochemical purity was determined by R-TLC using 3 eluents 90/10, 40-60 Petroleum ether/ diethyl ether, 95/5 40-60 Petroleum ether/diethyl ether and 100% dichloromethane. Total activity and specific activity were determined. Chemical Yield 4.5g (87%), Radiochemical Yield 97% Total Activity 13.13 mCi Specific Activity 3.015 uCi/mg Chemical Purity > 95% Radiochemical Purity 96%

Figure S4: ^{1}H NMR spectrum of 3

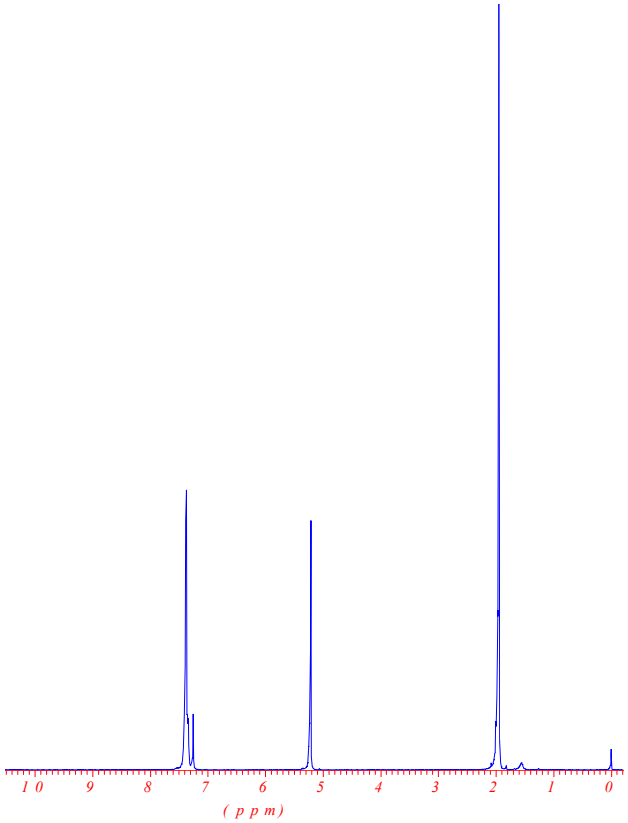
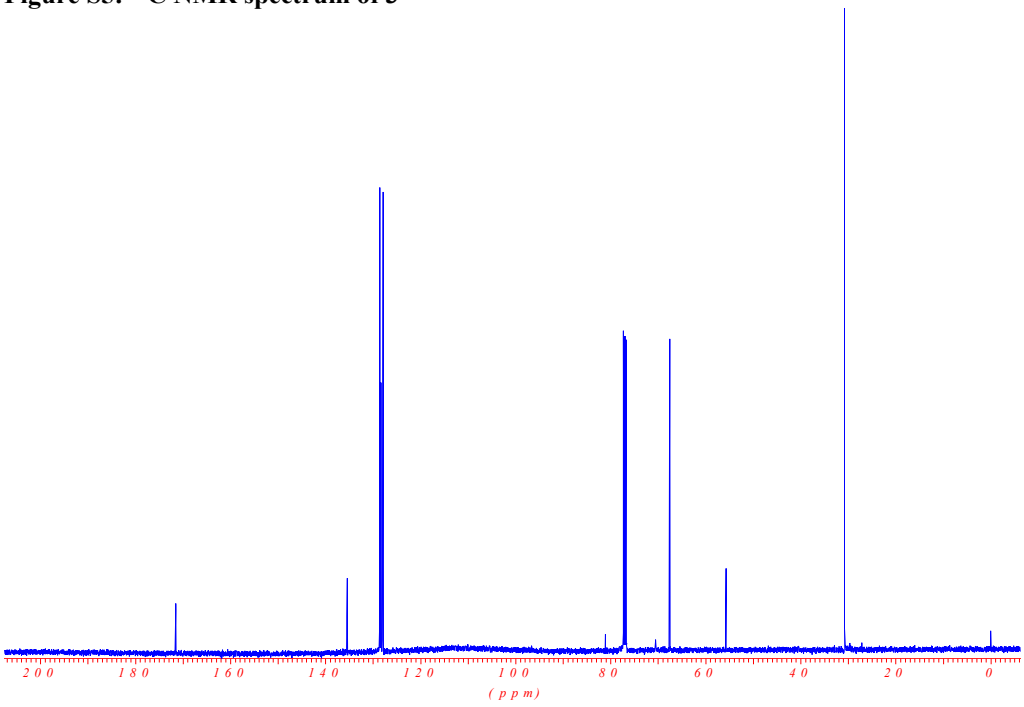


Figure S5: ^{13}C NMR spectrum of 3

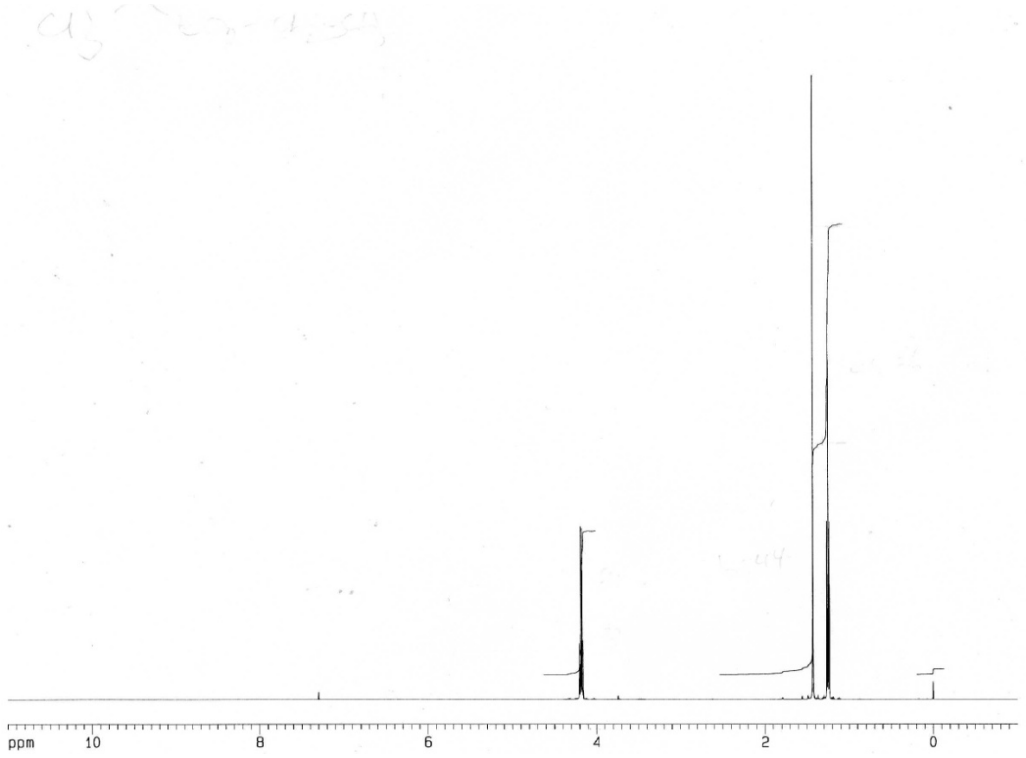


C) Synthesis of Non Labeled 2-bromo isobutyric acid

Step 1 Methylation of Diethyl Methyl Malonate

To a 50ml one necked round bottom flask containing a magnetic stirrer was added of diethyl methyl malonate (5.9 mmol), sodium ethoxide (21% solution, 1.1eq) and ethanol (10ml) under nitrogen. The reaction mixture was stirred, and warmed to 50^0C for 30 minutes. The reaction mixture was then cooled to room temperature. Methyl iodide (8.38 mmol, 1.4 eq) was added. The flask was flushed with nitrogen, sealed and warmed to 50^0C for 4 hours. After cooling, the ethanol and unreacted methyl iodide were removed using a rotary evaporator. Dry diethyl ether was added to the residue and the sodium iodide was filtered to yield a clear crude solution of diethyl dimethyl malonate. The diethyl ether was washed with water to remove residual sodium iodide. The diethyl ether layer was dried over magnesium sulphate, filtered and evaporated to yield a clear bronze coloured liquid. The structure and chemical purity of the final product was confirmed by ^{1}H NMR Chemical Yield 0.81g (73%), Chemical Purity > 95%

Figure S6: ^{1}H NMR spectrum of diethyl dimethyl malonate



Step 2 Hydrolysis of diethyl dimethyl malonate

To the diethyl dimethyl malonate, was added 2.4eq of an aqueous solution of Potassium Hydroxide (10ml). The solution was warmed to 80^0C with stirring until the oil was completely dissolved.

Step 3 Decarboxylation of the di-Potassium salt of dimethyl malonate

To the aqueous solution of the di-Potassium salt of dimethyl malonate was added an aqueous solution of sulphuric acid(2.4 eq, 20ml). The mixture was refluxed for five hours. The resulting isobutyric acid was recovered via distillation (azeotroped with water). To the water/isobutyric acid mixture potassium hydroxide was added (1.2eq). The solution was then freeze dried to yield potassium isobutyrate

Step 4 Bromination of Potassium Isobutyrate

Dry dichloroethane (30ml) and hydrochloric acid (2 eq) were added to the 50ml round bottomed flask containing the potassium isobutyrate. The reaction mixture was stirred for one hour at ambient temperature and purged with nitrogen. Chlorosulphonic acid (0.75 eq) and bromine (1 eq) were added. The reaction mixture was refluxed under nitrogen for six hours, then evaporated to remove solvent, excess hydrochloric acid, and residual bromine. The oil was redissolved in diethyl ether and washed with water to remove residual bromine and free propanoic acid. The ether was dried over magnesium sulphate, filtered and evaporated. The structure and purity of the final product, 2-bromo isobutyric acid, was confirmed by ^{1}H NMR and ^{13}C NMR. Overall Chemical Yield 550mg (56%).

Figure S7: ^{1}H NMR of 2-Bromo isobutyric acid

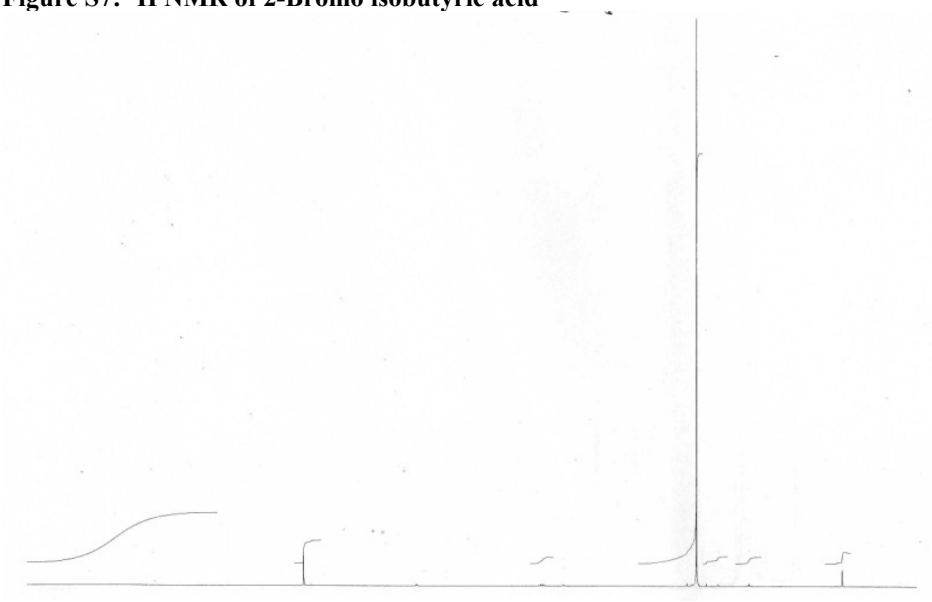
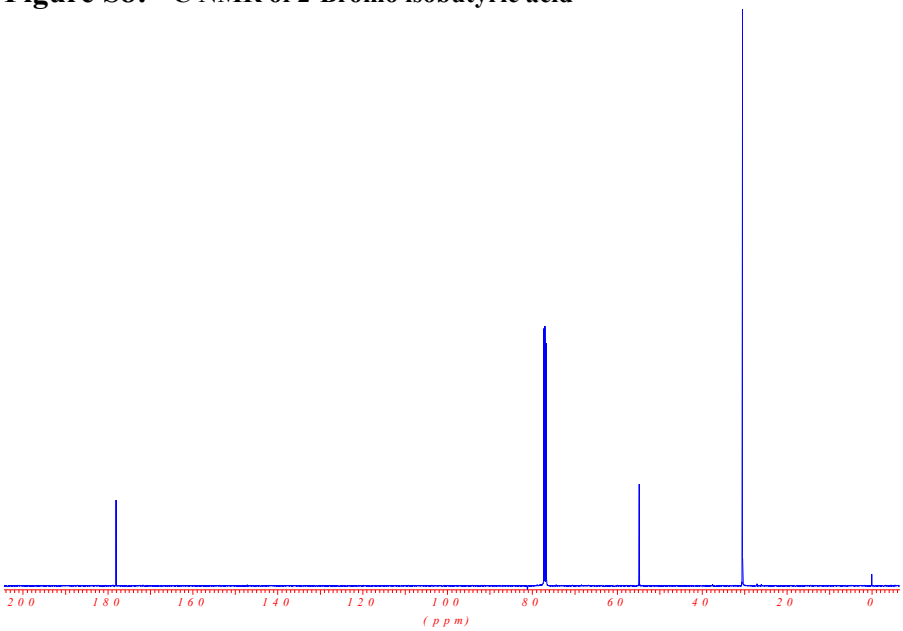


Figure S8: ^{13}C NMR of 2-Bromo isobutyric acid

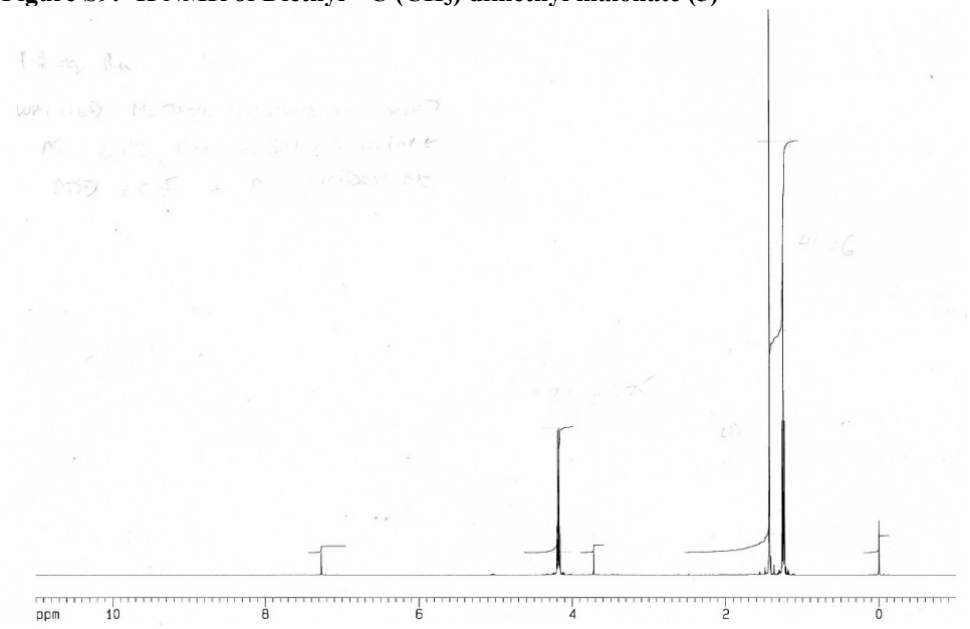


D) Synthesis of 2-Bromo ^{14}C (CH_3) isobutyric acid (11)

^{14}C (CH_3) Methylation of diethyl methyl malonate

To a 50ml one necked round bottom flask containing a magnetic stirrer was added of diethyl methyl malonate (5.9 mmol), sodium ethoxide (21% solution, 1.1eq) and ethanol (10ml) under nitrogen. The reaction mixture was stirred under a nitrogen atmosphere, and warmed to 50^{0}C for 30 minutes. The reaction mixture was left to cool to room temperature. Methyl iodide was added in two aliquots (initial addition 10 mCi/0.18mmoles of ^{14}C-metyhyl iodide (8.38 mmol, 1.4 eq) from a sealed ampoule followed by non-labelled methyl iodide (8.2mmoles)). The flask was flushed with nitrogen and warmed to 50^{0}C for 4 hours. Solvent and unreacted methyl iodide were removed via evaporation. Dry diethyl ether was added to the residue and the sodium iodide was filtered to yield a clear crude solution of diethyl ^{14}C (CH_3) dimethyl malonate. The diethyl ether was washed with water to remove any residual sodium iodide. The collected diethyl ether layers were dried over magnesium sulphate, filtered and evaporated to yield a clear bronze coloured liquid. Chemical Yield 76%, Radiochemical Yield 81% Total Activity 8.13 mCi Specific Activity 9.64 uCi/mg Chemical Purity > 95%

Figure S9: ^{1}H NMR of Diethyl ^{14}C (CH_3) dimethyl malonate (5)



Subsequent steps were repeated as above to produce 2-bromo ^{14}C (CH_3) isobutyric acid, as confirm by NMR and R-TLC. The total activity and specific activity were also determined. Chemical Yield 35%, Radiochemical Yield 54% Total Activity 5.4 mCi Specific Activity 15.6 uCi/mg Chemical Purity > 95% Radiochemical Purity 99%

Figure S10: ^{1}H NMR of 2-Bromo ^{14}C (CH_3) isobutyric acid (8)

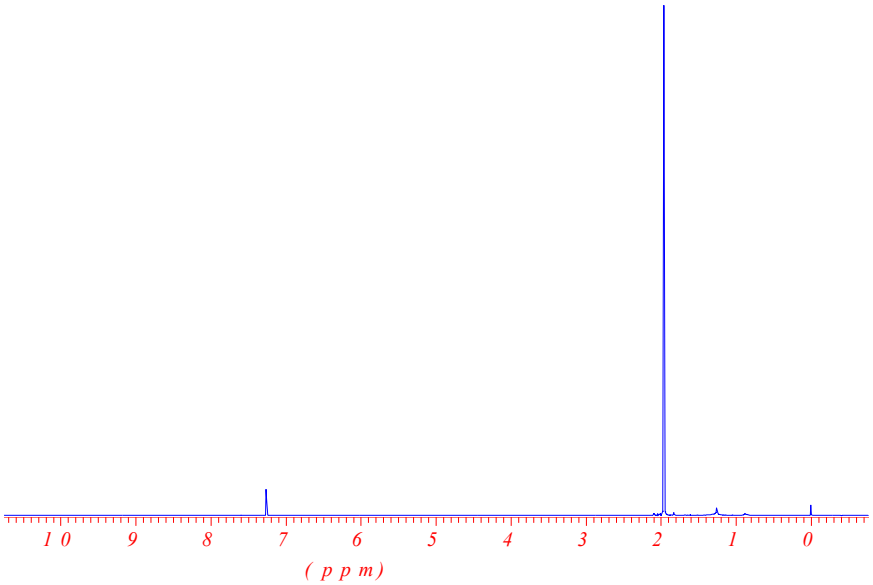


Figure S11: ^{13}C NMR of 2-Bromo ^{14}C (CH_3) isobutyric acid (8)

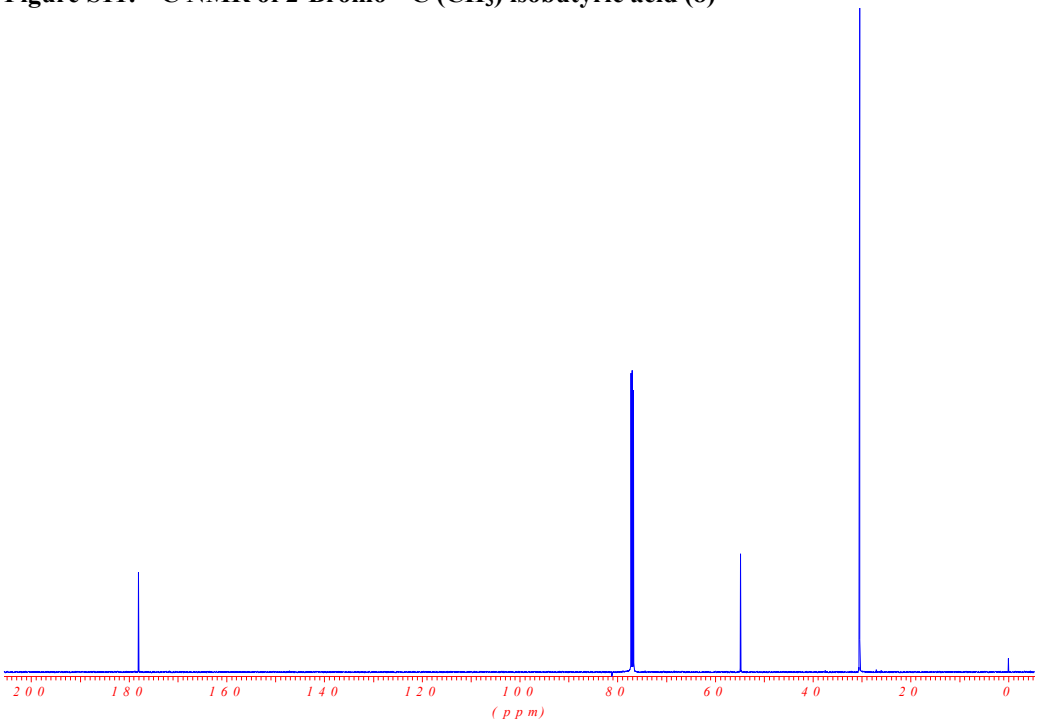
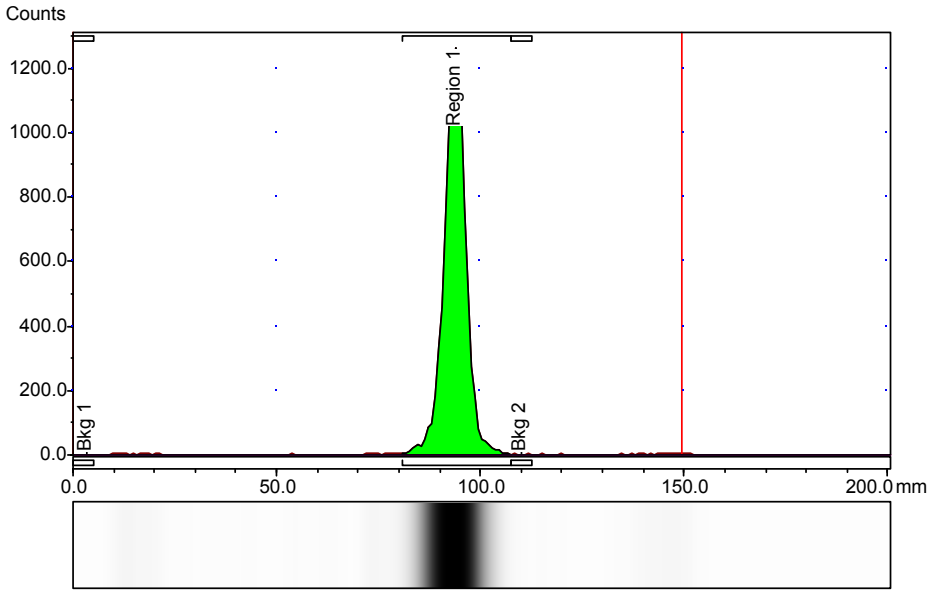


Figure S12: Radioanalytical TLC of Bromo ^{14}C (CH_3) isobutyric acid (8)



Synthesis of Benzyl 2-bromo ($^{14}CH_3$) isobutyrate (11)

To a 2 necked 50ml round bottomed flask was added 2-bromo isobutyric acid (2-bromo ($^{14}CH_3$) isobutyric acid (0.00051mol) and of non labelled 2-bromo isobutyric acid (0.00729mol)) and dry Tetrahydrofuran (25ml). The reaction mixture was warmed under nitrogen to 60^0C then 1,1'-carbonyldimidazole (1.0eq) was added. The mixture was stirred and heated under nitrogen at 60^0C until the 1,1'-carbonyldimidazole was totally dissolved and the effervescence (liberation of CO_2) ceased. At this point, benzyl alcohol (1.0eq) was added and the reaction mixture left to reflux for 4 hours. The reaction mixture was evaporated and the residue was redissloved in diethyl ether. The crude product was first washed with dilute hydrochloric acid followed by washing with aqueous sodium carbonate. The water layers were further extracted with diethyl ether. All diethyl ether layers were combined and dried over sodium sulphate, filtered and evaporated to yield a water clear oil. The structure of the final product, Benzyl 2-bromo ($^{14}CH_3$) isobutyrate was confirmed by ^{1}H NMR and ^{13}C NMR and the chemical and radiochemical purities determined by ^{1}H NMR and R-TLC using 3 eluents 90/10, 40-60 Pet Ether: Ether, 95/5 40-60 Pet Ether;Ether and 100% Dichloromethane The total activity and specific activity determined. Chemical Yield 1.1g (55%), Radiochemical Yield 56%, Total Activity 0.397mCi, Specific Activity 0.362uCi/mg, Chemical Purity 97%, Radiochemical Purity 98%

Figure S13: ^{1}H NMR of Benzyl 2-bromo ($^{14}CH_3$) isobutyrate (11)

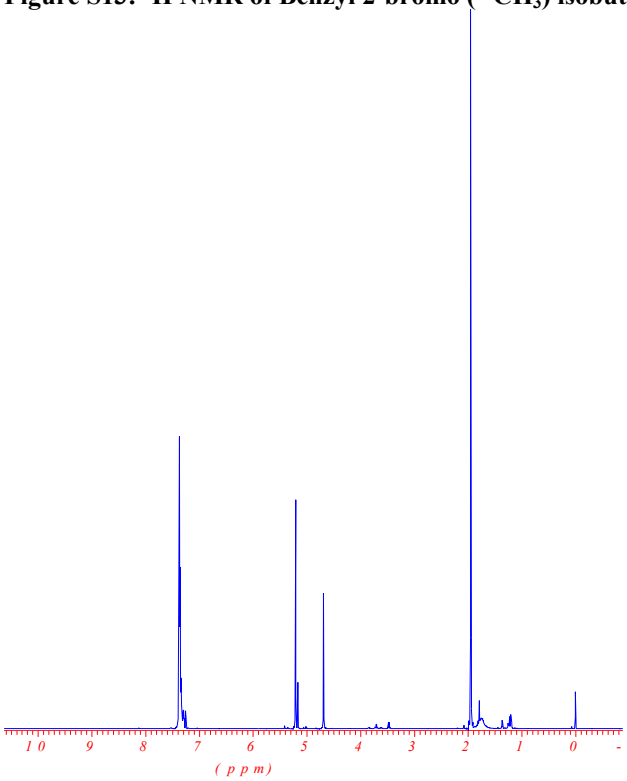


Figure S14: ^{13}C NMR of Benzyl 2-bromo ($^{14}CH_3$) isobutyrate (11)