The Radiosynthesis of No-Carrier Added [1-^{11}C]Allyl Alcohol Evidence for the Formation of a New Reducing Species: Lithium Aluminium Hydride - Vinylmagnesium Bromide

Marie-Claire Lasne[a*], Bernard Moreau[a], Philippe Cairon[a] and Louisa Barré[b]

[a]*URA CNRS D 0480, Institut des Sciences de la Matière et du Rayonnement, Université de Caen - Basse Normandie, 6 Boulevard du Maréchal Juin, 14050 Caen;*
[b] *CEA, DSV/DPTE Centre Cyceron, Boulevard Henri Becquerel, 14074 Caen, France*

Summary

Lithium aluminium hydride in the presence of vinylmagnesium bromide (1:1 molar ratio) affords a potent reagent for the reduction of acrylic acid to allyl alcohol (ratio of allyl alcohol to 1-propanol: 3:2). This reducing mixture has allowed the preparation of no-carrier added [1-^{11}C]allyl alcohol with a 25% yield (decay corrected at the end of radionuclide production, overall synthesis time including GC: 40 min) in a one step procedure from [^{11}C]carbon dioxide (C-11: $t_{1/2}$: 20.4 min). [1-^{11}C]1-propanol was obtained in parallel with a 6.5% yield.

Key words: [1-^{11}C]allyl alcohol, [1-^{11}C]acrylic acid, reduction, lithium aluminium hydride - vinylmagnesium bromide

* Author for correspondence

Introduction

The selective reduction of α, β-unsaturated carboxylic acids to the corresponding allylic alcohols remains a challenging problem because of the poor reactivity of the carboxyl group and the possible reduction of the double bond with powerful reducing agents (1). Various systems have been developed for the reduction of conjugated

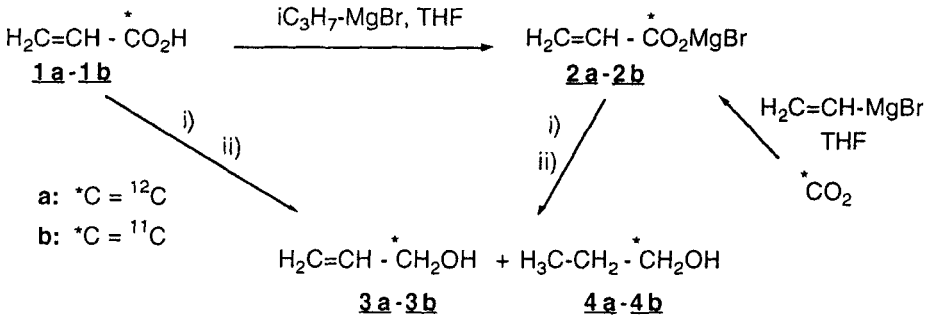
CCC 0362–4803/94/121165–10

Received 24 May, 1994
Revised 15 August, 1994

ketones and aldehydes but only a few exist for α, β-unsaturated acids [$NaBH_4$/*N,N*-dimethylchloromethyleniminium chloride (2) $NaBH_4/I_2$ (3)] and esters [diisobutylaluminium hydride (DIBALH) (4)]. For chemoselective reductions, carboxylic acids are generally converted into reactive derivatives and then reduced by a weak reducing agent (2). With the aim of synthesizing new ligands labelled with carbon-11 (β^+ emitter) for *in vivo* studies of their biodistribution and pharmacokinetics by positron emission tomography, we required an efficient synthesis of [1-^{11}C]allyl alcohol **3b** from [1-^{11}C]acrylic acid **1b**. The alcohol **3b**, in an activated form (5) or used in catalytic reactions (6) could be a useful reagent for the introduction of a ^{11}C-allyl group in molecules of biological interest such as naloxone, a selective antagonist of opioid receptor (7). Because of the short half-life of carbon-11 ($t_{1/2}$: 20.4 min) and the low amount of non-radioactive carbon dioxide co-produced by the cyclotron (~ μmol), the reduction of the acid **1b** must be rapid and chemoselective even when a large excess of reducing agent is used. Moreover, the final product has to be easily extracted and purified (8). ^{11}C-Alcohols are generally prepared (8) by reduction of the corresponding metallic carboxylate with lithium aluminium hydride (LAH) a well-known powerful reducing agent, capable of reducing many functional groups. The reaction of acrylic acid **1a** with LAH (9) led exclusively to 1-propanol **4a** probably *via* an internal hydride transfer (10). The preparation of [1-^{14}C]allyl alcohol from the corresponding acid or ester required either the protection of the double bond (9) or a multistep synthesis (11). Improvements of the selectivity of the reductions can be achieved by modification of the steric and electronic effects of the substituents on the aluminium atom [*i.e.*: lithium tri-*tert*-butoxy aluminium hydride (12), or the complex generated from equimolar amount of DIBALH and *n*-butyllithium (13)]. Such an improvement can also be expected from the use of LAH in the presence of organometallic species. It has been reported that LAH reacts with organolithiums or Grignard reagents (14) to give a mixture of complex hydrides, which have never been used as reducing agents.

We now wish to report a rapid and selective reduction of acrylic acid **1a** (or of its salt **2a**) to allyl alcohol using an equimolar mixture of LAH and vinylmagnesium bromide. This reagent has allowed the preparation of [1-^{11}C]allyl alcohol **3b** from no-carrier added cyclotron-produced [^{11}C]carbon dioxide in a one pot procedure, avoiding either the protection of the double bond of acrylic acid or a multistep synthesis (scheme 1).

Scheme 1



i) reducing agent ii) HCl, H_2O

Experimental

General

NMR spectra were recorded on a Brucker WP80 SY3 spectrometer (20.15 MHz for ^{13}C NMR, 20.88 MHz for ^{27}Al NMR). TMS was used as internal standard for ^{13}C NMR and aluminium sulfate for ^{27}Al NMR. Negative chemical shifts of ^{27}Al are given for aluminium atoms at higher field than the reference. GC analyses of non radioactive mixtures were obtained on a Girdel chromatograph equipped with an ionization flame detector and a fused silica capillary column (25 m x 0.32 mm). Preparative radioactive GC separations were conducted on a Delsi chromatograph equipped with a column packed with Carbowax 20M, a thermal conductivity detector and a "Nardeux IPM 10" radioactive detector. Identification of the labelled compounds was made by co-elution with 1-5 µL of standard. The ^{11}C-alcohols were collected in a trap cooled in liquid nitrogen. Radioactivity determinations were carried out by a Capintec Radioisotope Calibrator (CRC).

DIBALH (1.0 M solution in cyclohexane), Red-Al (3.4 M solution in toluene) and all standard chemicals were purchased from Aldrich Chemical Co or Janssen Chimica. Molar solution of LAH (15), aluminium hydride (16), phenyl, propyl, isopropylmagnesium (17) and vinylmagnesium bromides (18) were prepared according to described procedures. Magnesium bromide acrylate **2a** was prepared by stirring for 30 min, under nitrogen, acrylic acid (6.56 mmol) in THF (6ml) with isopropylmagnesium bromide (7.3 mL, 0.9 M in THF).

General procedure for the reduction of acrylic acid **1a** *or of its salt* **2a**.

Method A: The reducing agent in the given solvent (see table 1) was added at - 70°C to a stirred solution of acrylic acid **1a** (or of its salt **2a**, 7 mmol) in THF (7 mL) containing eventually a Grignard reagent (7 mmol). The mixture was stirred for 20 min at -70°C then 10 min at 25°C. After evaporation of the solvent under reduced pressure, the mixture was hydrolyzed with HCl 2M (4 mL) and the alcohols extracted with diethyl ether (3x10 mL). The organic layers were dried over magnesium sulfate and concentrated to 2 mL by distillation. The residue was analysed by NMR and GC. The ratios **3a**: **4a** are shown in Table 1.

Method B, Methods C and D: see table 1. After reaction, the mixture was treated and analysed as in method A.

Reduction of [1-^{11}C]magnesium bromide acrylate **2b**: [^{11}C]Carbon dioxide was produced by the ^{14}N[p,α]^{11}C nuclear reaction with a CGR MeV 325 baby cyclotron. Bombardment was carried out for 1-2 min with a 2 μA beam of 16 MeV protons. At the end of radionuclide production (reference time) the target was vented into a loop (60 μL) of stainless steel tube (0.51 mm i.d.) that has been pre-flushed with dry nitrogen and immersed in liquid argon. This operation which takes about 5 min gave approximately 170-300 MBq of [^{11}C]CO_2. This latter was trapped at 0°C by vinylmagnesium bromide (300 μL, 0.5 M in THF)(19) and allowed to react for 3 min at 0°C and 2 min at 25°C to give the [1-^{11}C]magnesium bromide acrylate **2a**. The reaction vessel was rapidly cooled to -70°C and the reducing agent (50 μmol) was added. After stirring with a nitrogen flow (10 mL min^{-1}) for 1-2 min at this temperature, the cooling bath was removed and the mixture stirred for 1-3 min at 25°C. After evaporation of the volatile compounds under vacuum (12 Torr, 3 min), the salts were hydrolysed by adding aqueous HCl (400 μL, 0.1 M) and the aqueous layer extracted with diethyl ether (3 x 0.8 mL). The organic layer was dried by passing through a small column (20 x 10 mm) filled with Na_2SO_4. The crude radiochemical yields (> 15 runs) were about 35-45% (decay corrected to the end of radionuclide production). The reaction mixture was analysed and purified by GC (Carbowax 20M, 10%, oven temperature: 70°C, He flow rate 250 mL.min^{-1}; figure 1). [^{11}C]Methanol formed (0 - 35% yield) was eluted first (tr:

2.5 min) followed by [1-^{11}C]1-propanol **4b** (tr: 6.5 min, 4 - 6.5%) and [1-^{11}C]allyl alcohol **3b** [tr: 11.5 min, 15 - 25%, 40 min] (All the yields are given from [^{11}C]CO_2). After 15 min at 70°C, the GC column was heated at 170°C (15°C.min^{-1}) to elute unreacted [^{11}C]acrylic acid. Because of the small amounts of radioactivities used, no measurement of the specific radioactivities has been carried out. From our previous results (19), starting from 300 MBq of [^{11}C]CO_2 [^{11}C]acrylic acid was formed with a specific radioactivity of 500 MBq/μmol.

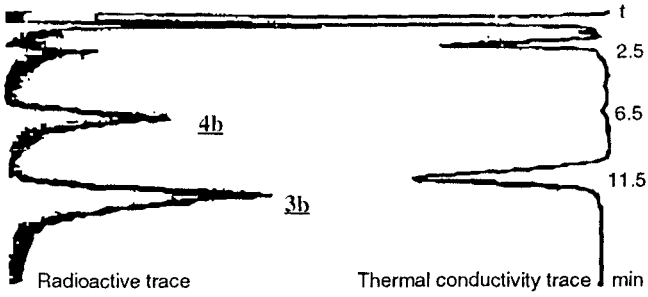


Figure 1 Reduction of **2b** with LAH/H_2C=CHMgBr : GC of the crude reaction mixture co-eluted with allyl alcohol **3a**.

Results and Discussion

In a typical procedure (A), the acid **1a** or its salt **2a** (preformed by reaction of **1a** with isopropylmagnesium bromide) was treated with the reducing agent for 20 min at -70°C and 10 min at 20°C. After work up, ^{1}H NMR and GC analysis showed the exclusive formation of the two expected alcohols **3a** and **4a**. Due to their partial solubility in water and the difficulty of completely removing the solvent, no attempt was made to determine the isolated yield in non radioactive experiments. As shown in Table 1, 1-propanol **4a** was the major product formed in the reductions even when DIBALH or AlH_3 were used *(entries 1-5)*. As expected from the literature results, the allyl alcohol ratio increased either when using toluene as the solvent *(entry 2)*, aluminium hydride *(entry 3)* as the reducing agent, or when the reaction was carried out preferably onto the salt **2a** *(entries 3,5,* figures in square brackets). When the reduction with LAH in THF was carried out in the presence of isopropylmagnesium bromide, we noticed that the ratio **3a** to **4a** reached 1: 2.5 *(entry 8)*. This prompted us to examine the *reduction of*

acrylic acid (free or as a salt) in the presence of various Grignard reagents. The best results (Table 1) were obtained either with vinyl *(entry 11)* or phenyl *(entry 20)* magnesium bromide and when LAH was allowed to react with the Grignard reagent for a few hours before addition of the carboxylic derivative *(entries 14, 15)*. Under the conditions used in methods C or D, a 1: 1 molar ratio of LAH and Grignard reagent led

Table 1: Reduction of Acrylic Acid **1a** [or of the salt **2a**].

Entry	Method [a]	Reagent[b]	Molar ratio [c]	ratio [d,e] allylalcohol/1-propanol **3a: 4a**	
1	A	LAH	1	1: 10 -1: 19	[1: 7]
2	A	LAH (toluene)	1	1: 2.3	
3	A	AlH_3	1.2	1: 1.4	[1:1]
4	A	DIBALH (cyclohexane)	2.2	1: 1.9	
5	A	Red-Al (toluene)	2.6	1: 1.8	[1: 1.3]
6		$NaBH_4$ / $ClCH=N^+(CH_3)_2$, Cl^- [f]	2:1	1: 1	
7		$NaBH_4$ / I_2 [g]	1.2: 0.5	1: 5.3	
8	A	LAH / iC_3H_7MgBr	1.1: 1.1	1: 2.5	
9	A	LAH / $H_2C=CHMgBr$	1.1: 0.33	1: 1.7	
10	A	LAH / $H_2C=CHMgBr$	1.1: 1.1	1: 2.2	[1: 1.3]
11	A	LAH / $H_2C=CHMgBr$	1.1: 4.4	3: 2	
12	B	LAH / $H_2C=CHMgBr$	1.1: 0.33	1: 5.6	
13	B	LAH / $H_2C=CHMgBr$	1.1: 1.1	1: 3	
14	C or D	LAH / $H_2C=CHMgBr$	1.1: 1.1	3: 2	
15	D	LAH / $H_2C=CHMgBr$	1.1: 4.4	3: 2	
16	A	LAH / C_3H_7MgBr	1.1: 0.5	1: 15	
17	A	LAH / C_3H_7MgBr	1.1: 1.1	1: 6.1	[1: 5.2]
18	A	LAH / C_6H_5MgBr	1.1: 0.33	1: 3	
19	A	LAH / C_6H_5MgBr	1.1: 1.1		[1: 1.5]
20	A	LAH / C_6H_5MgBr	1.1: 4.4	1.3: 1	
21	A	LAH / MgI_2	1.1: 1.1	1: 5.6	
22	A	LAH / MgI_2	1.1: 4.4	1: 2.3	
23	A	LAH / $H_2C=CHMgBr/CeCl_3$	1.1: 1.5: 1.5	1: 1.3	

[a] Method A: LAH was added at -70°C to a mixture of **1a** and RMgX; Method B : RMgX and LAH were mixed and stirred for 20 min at 0°C and cooled to -70°C for the addition of **1a**; methods C, D: LAH and RMgX were stirred for 4h (method C) or 15h (method D) at 0°C before adding **1a** at -70°C. [b] All the reactions were carried out in THF unless otherwise stated. [c] for 1 mole of **1a** (or **2a**). [d] determined by GC; [e] the figures in square brackets refer to reductions carried out on the salt **2a**. [f] under the conditions described in ref. (2) [g] under the conditions described in ref. (3)

to a selectivity comparable to that obtained in method A *(entry 11)*, using 4 moles of organomagnesium reagent per mole of hydride.

No improvement on the selectivity was observed by using more than one molar excess of Grignard reagent in method C or D. The addition of cerium trichloride (20) *(entry 23)* or the use of magnesium iodide instead of a Grignard reagent *(entries 21, 22)* have no important effect on the selectivity.

Finally, LAH/H_2C=CHMgBr was compared to other reagents known to be selective of the reduction of the carboxyl group of an α, β-unsaturated acid. Under the conditions described in the literature, acrylic acid led to 1-propanol (up to 84%) with $NaBH_4/I_2$ (3) whereas $NaBH_4$/*N,N*-dimethylchloromethyleniminium chloride (2) afforded a 1: 1 mixture of the alcohols **3a** and **4a**.

Without trying to elucidate the exact structure of the reducing mixture, a solution of LAH and H_2C=CHMgBr (1: 1 molar ratio, in THF) was analysed by NMR. ^{27}Al NMR detected a single species exhibiting an unsplit broad singlet at -121 ppm relative to $[Al(H_2O)_6]^{3+}$ (- 97 for LAH) (21). ^{27}Al NMR of solutions containing LAH with the Grignard reagent in excess showed the same chemical shifts (±1 ppm). The comparison of the chemical shifts of the carbon of this LAH and H_2C=CHMgBr reagent (δ_{TMS}: 130.9 and 129.6) with those observed in H_2C=CHMgBr (δ_{TMS}: 169.3 and 130.1) showed an important upfield shift (38 ppm) in the signal due to the carbon attached to the metallic atom.

The selectivity we observed led us to attempt the preparation of [1-^{11}C]allyl alcohol by reduction of the salt **2b** of [1-^{11}C]acrylic acid. Because of the low amount of salt **2b** which is formed from $[^{11}C]CO_2$, all the reductions were carried out in the presence of a large excess of H_2C=CH-MgBr. GC analysis of the crude reaction mixture showed the presence, with the expected ^{11}C-alcohols **3b** and **4b**, of $[^{11}C]CH_3OH$ (from $[^{11}C]CO_2$ which was not trapped by the Grignard reagent) and of unreacted [^{11}C]acrylic acid (from 14 to 40%). However no other side products were detected. In Table 2, we have compared the ratios **3b**: **4b** and the isolated radiochemical yields when the reaction was carried out under different conditions. Again the highest selectivity was obtained when using LAH. Optimization of the reaction time and temperature allowed the reproducible preparation of [1-^{11}C]allyl alcohol in 15 - 25% yield and [1-^{11}C]1-propanol (4 - 6.5 %) from $[^{11}C]CO_2$ in 40 min total synthesis time (from the end of radionuclide

production). The structure of the alcohols **3a** and **4a** was assigned on spectroscopic data (^{1}H and ^{13}C, IR) and the formation of the different radioactive compounds (**1b**, **3b** and **4b**) was confirmed by comparison of their retention times in GC (see experimental part) and co-elution with standards.

Table 2 : Selectivity of the Reduction of [^{11}C]Magnesium Bromide Acrylate **2b** with Different Reducing Agents.

entry	reducing agent [a]	time (min) [temp. (°C)]	ratio[b] **3b**: **4b**	yield (%)[c]
24	LAH	1.5 [-70] then 2 [25]	3: 1	25
25	AlH_3	1.0 [-70] then 2.0 [0]	1: 1.8	9
26	Red-Al	1.0 [-70] then 1.0 [0]	2: 1	12
27	DIBALH	1.0 [-70] then 1.0 [0]	1.2: 1	9

[a] the reactions were carried out in THF *(entries 24, 25)*, toluene *(entry 26)* or cyclohexane *(entry 27)* with 50 µmol of reducing agent and 150 µmol of vinylmagnesium bromide. [b] determined by GC. [c] isolated, decay corrected to the end of radionuclide production.

In conclusion, [1-^{11}C]allyl alcohol can be easily prepared by a "one-pot" reaction of LAH with [1-^{11}C]acrylic acid. It was shown that LAH in the presence of an unsaturated Grignard reagent gives a new efficient and selective reducing species. The ready availability of this latter should encourage its use for the reduction of more complex α, β–unsaturated acids. Further studies on reaction of LAH / vinylmagnesium bromide with polyfunctional compounds are in progress.

References

1. For reviews on the reductions and reducing agents see: (a) Brown H.C. and Krishnamurthy S. - Tetrahedron 35: 567 (1979). (b) Seyden-Penne J. - "Réduction par les alumino et borohydrures en synthèse organique" Technique et Documentation Lavoisier, Paris, pp 66-74 (1988). (c) Hudlicky M. - "Reductions in Organic Chemistry" Horwood, Chichester, pp 136-138 (1984). (d) Barret A.G.M. -

"Comprehensive Organic Synthesis", Trost B.M. and Fleming I. Eds, Pergamon Press, London, Vol 8, pp 236-244 (1991). (e) Walker E.R.H. - Chem. Soc. Rev. 23 (1976). (f) Larock R.C. - "Comprehensive Organic Transformations" VCH. Publishers, Cambridge, pp 548-552 (1989).

2. Fujisiwa T., Mori T. and Sato T. - Chem. Lett. 835 (1983) and references cited therein .

3. Kanth J.V.B. and Periasamy M. - J. Org. Chem 56: 5964 (1991).

4. Winterfeld E. - Synthesis 617 (1975).

5. Preliminary communications: (a) Lasne M.C., Cairon Ph., Barré L., Moreau B. and Pike V.W. - J. Label. Cmpds. Radiopharm. 30: 129 (1991). (b) Lasne M.C., Moreau B., Barré L., Cairon Ph. and Ducandas C. - J. Label. Cmpds. Radiopharm. 32: 180 (1993).

6. For some examples: (a) Trost B.M. - Tetrahedron 2615 (1977). (b) Tsuji J. - Synthesis 739 (1990).

7. Bradley P.B. - "Introduction to Neuropharmacology" Wright, London, p. 258 (1989).

8. Fowler J.S.and Wolf A.P. - "Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart" Phelps M., Mazziotta J. and Schelbert H. Eds, Raven Press, New York, pp 391-450 (1986).

9. Pichat L., Herbert M. and Aubert F. - J. Label. Cmpds Radiopharm 1: 66(1965).

10. See for example : (a) Snyder E.I. - J. Org. Chem. 32: 3531 (1967). (b) Vincens M., Fadel R. and Vidal M. - Bull. Soc. Chim. Fr. 462 (1987).

11. Kupczyk-Subotkowska L. and Shine H.J. - J. Label. Cmpds Radiopharm. 31: 381 (1992).

12. Malek J. and Cerny M. - Synthesis 217 (1972).

13. Kim S. and Ahn K.H. - J. Org. Chem. 49: 1717 (1984).

14. Ashby E.C. and Schwartz R.D. - Inorg. Chem. 11: 919 (1972).

15. Fieser L.F. and Fieser M. - "Reagent for Organic Synthesis" J. Wiley and Sons, London, Vol 1, 581 (1967).

16. Jorgenson M.J. - Tetrahedron Lett. 559 (1962).

17. Vogel's "Textbook of Practical Organic Chemistry" IVth Ed , Longman Scientific & Technical, New York, p 326, p 369 (1987).

18. Normant H. and Maitte P. - Bull. Soc. Chim. Fr. 1439 (1956).

19. Lasne M.C., Cairon Ph. and Barré L. - Appl. Radiat. Isot. 43: 621 (1992).

20. Gemal A.L. and Luche J.L. - J. Amer. Chem. Soc. 103: 5424 (1981).

21. Hermanek S., Kriz O., Plesek J. and Hanslik T. - Chem. Ind. (London) 42 (1975).