Rapid synthesis of aliphatic amides by reaction of carboxylic acids, Grignard reagent and amines: application to the preparation of [^{11}C]amides

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Aliphatic amides have been prepared in moderate to good yields (30–70%) by treatment in THF of magnesium halide carboxylates with amines in the presence of 2.5 equivalents of alkylmagnesium halide. The reaction is rapid (<30 min) and has been successfully applied to the synthesis of amides labelled with carbon-11 (β^+, $t_{\frac{1}{2}}$: 20.4 min). [^{11}C]Aliphatic amides have been obtained in 15–60% radiochemical yields [decay corrected to end of bombardment (EOB), 5 min amidation reaction time].

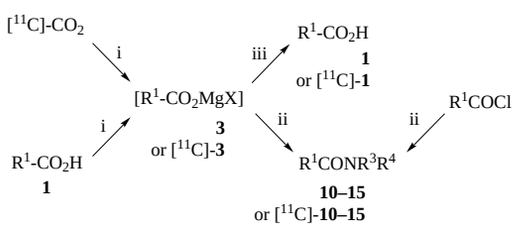
Introduction and background information

The development of *in vivo* studies of biological processes in living animals or humans using positron emission tomography (PET) is strongly dependent on the availability of new tracers labelled with a positron emitter such as carbon-11, fluorine-18, oxygen-15 or nitrogen-13. Although carbon-11 is the most widely used radioisotope, radiosyntheses of ^{11}C-compounds are always a challenge. Only two cyclotron-produced labelled precursors are available ([^{11}C]CO_2 and [^{11}C]CH_4). Due to the short half-life (20.4 min), preparation of ^{11}C-labelled compounds require minimum-step synthesis, very rapid and efficient reactions and simple handling and transfers. Moreover, specific activity, stoichiometry, purification methods and radiation protection are additional considerations.[1]

A large variety of radiopharmaceuticals include an amide[2–5] or an amine function. This latter is often obtained by reduction[6,7] or by pyrolysis[8,9] of the suitable amide. Several [^{11}C]-alkylamides,[10–12] cyclopropanecarboxamide,[10,11] acrylamides,[13] benzamide[14] and *N*,*N*-disubstituted benzamides[15] have been described. The preparations are based on two different approaches. In the first one, [^{11}C]CO_2 is trapped with a Grignard reagent and the resulting [^{11}C]carboxylate is then transformed into an [^{11}C]acid chloride[2–9,10–13] or into an activated form of the [^{11}C]acid[15] before its reaction with an amine. This method requires at least three steps from [^{11}C]CO_2. In the second route, [^{11}C]benzonitrile, obtained by a palladium-catalysed reaction of [^{11}C]cyanide anion with bromobenzene, is hydrolysed. This route leads only to non-substituted [^{11}C]benzamide.[14] Among the readily available labelled precursors, [^{11}C]-carboxymagnesium halides are attractive by being obtained efficiently by carboxylation of Grignard reagents with [^{11}C]-CO_2.[16–18] Up to now, they were only used as intermediates for preparing labelled reagents such as [^{11}C]carboxylic acids,[18–20] [^{11}C]acid chlorides[2–9,10–13] or [^{11}C]alkyl iodides[19,21–26] *via* the corresponding alcohols. Development of a new general synthetic procedure for the preparation of amides using directly the [^{11}C]carboxylates as reactive intermediates is therefore essential.

In stable isotope chemistry, many procedures to obtain amides from carboxylic acids are known.[27–29] The most common methods are based on the conversion of the acid into a more reactive functional intermediate (isolated or formed *in situ*[29,32]) like an acyl chloride, mixed carboxylic anhydride, acyl azide or active ester before reaction with an amine. The direct reaction between an acid itself and a free amine is of limited scope due to the high temperatures it requires.[30,31] Several metallic compounds used in catalytic[29,33–36] or stoichiometric[29,37–42] amounts, have also been found to promote amidations. Recently, zirconium(IV), titanium(IV) or tantalium(V) carboxylates were isolated and transformed into amides in good yields.[40,41] In some other cases, amines were activated as organometallic complexes.[43–51]

Recently, we observed that the direct reaction of the [^{11}C]acetate and butanoate with 1,2,3,4-tetrahydroisoquinoline yielded the corresponding [^{11}C]amides.[52] To our knowledge, such a reactivity of carboxymagnesium halides towards amines for amides synthesis has never been studied. Here we report our results for the one-step conversion of carboxymagnesium halides into amides by reaction with a free amine both in stable isotope and carbon-11 chemistries (Scheme 1).



R^1-CO_2H **1**, R^1MgX or R^2MgX **2**

	a	b	c	d	e	f
R^1 or R^2	Pr	Et	Me	Pr^i	Bu^t	Ph

R^3R^4NH	$R^1CONR^3R^4$
1,2,3,4-Tetrahydroisoquinoline **4**	**10**
Butanamine **5**	**11**
Dipropylamine **6**	**12**
Morpholine **7**	**13**
Aniline **8**	**14**
1-Phenylethylamine **9**	**15**

Scheme 1 *Reagents:* i, R^1MgX or R^2MgX **2**; ii, R^3R^4NH **4**–**9**, then aq. HCl; iii, aq. NH_4Cl

Results and discussion

Amides in stable isotope chemistry

Carboxymagnesium halides **3** were prepared *in situ* by reaction of a Grignard reagent **2** with a carboxylic acid **1** at 70 °C in THF for 15 min. The Grignard reagent **2** was used in a stoichiometric amount or in excess compared to the acid **1** (Table 1). After addition of the amine **4**–**9**, the reaction mixture was treated under the conditions reported in Tables 2, 3 or 4. The structures of the different reaction products obtained after

Table 1 Amide **10a** from $PrCO_2H$ **1a** (2 mmol), PrMgBr **2a** and amine **4**.[a] Yields as a function of the ratio **2a**/**4**.

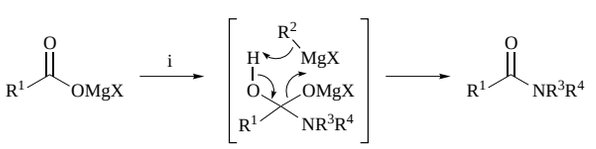
Entry	PrMgBr **2a** (mmol)	Amine **4** (mmol)	**10a** Yields[b] (%)
1	0	2	0
2	2	2	0
3	2	5	0
4	3	2	0
5	4	2	16
6	5	2	50
7	5	5	49
8	5	8	54
9	10	5	65
10	15	2	59

[a] In refluxing THF for 60 min. [b] Isolated yields.

hydrolysis were assigned from the spectroscopic data of pure isolated compounds. These reaction products were found to be the expected amides **10**–**15**, the starting amines **4**–**9** and traces of non-identified compounds. An independent synthesis of the expected amides **10**–**15** was also carried out using the acid chloride method to have authentic samples and spectroscopic data as references (Scheme 1).

The influence of the amounts of the organomagnesium halide and the amine was studied for optimizing the preparation of the amide **10a** from butanoic acid **1a** or its salt **3a** (pre-formed by reaction of propylmagnesium bromide **2a** with the acid **1a**) and tetrahydroisoquinoline **4**. All experiments were carried out in THF for 60 min (Table 1). As expected, no reaction was observed between the free acid **1a** and the amine **4**[30,31] (entry 1). The synthesis starting from the salt **3a** (obtained by reaction of 1 equivalent of the acid **1a** with 1 to 2 equivalents of propylmagnesium bromide **2a**) did not lead to the amide **10a** (entries 2, 3 and 4). Formation of the amide **10a** was effected when the ratio of Grignard reagent *versus* acid **1a** was higher than 2.5 (entry 6). Yields were not significantly improved by using a larger amount of Grignard reagent (entry 10) and they were not changed by using ethylmagnesium bromide instead of propylmagnesium bromide. The use of an excess of the amine **4** had no effect on the yields (entries 7 and 8) except when the reaction was carried out in presence of a large excess of Grignard reagent (entry 9).

The need to have a 1:1:1.5 molar ratio of carboxylate/amine/organomagnesium halide could be related to the conditions described for the preparation of amides from magnesium halide amide (2 mol equiv.) and ester (1 mol equiv.).[50,51] We suggest that the formation of the amide **10a** involves the intermediate **16** (Scheme 2). The latter, obtained by reaction of



3 **16** **10**

Scheme 2 *Reagents:* i, R^3R^4NH **4**–**9**, R^2MgX **2**

the carboxylate **3a** with the amine **4**, is decomposed by a nucleophilic attack of the alkylmagnesium halide present in excess according to a six-centred mechanism.

Classically, Lewis acids [$TiCl_4$, $Ti(Pr^iO)_4$, BBr_3, $AlCl_3$ *etc.*] used in catalytic or stoichiometric amounts[29,32–40] are known to be very efficient for the conversion of esters into amides, lactams or for transamidations. Attempts to use different Lewis acids (BCl_3, $ZnBr_2$, $HgCl_2$ or $TiCl_4$) in excess compared to the carboxylate **3a** failed. No amide **10a** was formed by reaction of the carboxylic acid **1a** (2 mmol) with tetrahydroisoquinoline **4** (2 mmol), ethylmagnesium bromide **2b** (5 mmol) and one of these Lewis acids (5–10 mmol) in THF for 60 min. The starting amine **4** was quantitatively recovered.

Table 2 Amide **10a** from $PrCO_2H$ **1a** (2 mmol), amine **4** (2 mmol) and EtMgBr **2b** (5 mmol).[a] Yields as a function of the solvent.

Entry	Solvent	**10a** Yields[b] (%)
1	THF	49–52
2	Et_2O	45
3	THF/Dioxane[c]	20
4	THF/DME[c,d]	15
5	THF/DMF[c,e]	0
6	THF/HMPA[c,f]	0

[a] At the reflux temperature of the solvent for 60 min reaction time. [b] Isolated yields. [c] THF/co-solvent = 70/30 (v:v). [d] Dimethoxyethane. [e] *N*,*N*-dimethylformamide. [f] Hexamethylphosphoramide.

The solvent effect on the yield of the amide **10a** was studied in the reactions using butanoic acid **1a** (2 mmol), tetrahydroisoquinoline **4** (2 mmol) and ethylmagnesium bromide **2b** (5 mmol) (Table 2). THF gave the best results compared to Et_2O and a mixture of THF–dioxane (entries 1, 2 and 3). Addition of a polar solvent[53] to THF inhibited the amidation (entries 4, 5 and 6).

The effect of the reaction time was studied in the syntheses of the amides **10a**, **10b**, **10c** and **11a** using a 2:2:5 molar ratio of acid/amine/Grignard reagent (Table 3, entries 1, 3, 5 and 6). Yields were found to be optimum in less than 30 min and often after 2–5 min only. When we increased the Grignard reagent amount, we observed that the best yields could be reached after a shorter reaction time (Table 3, entries 2 and 4).

Finally, the scope of the reaction was studied and some results are presented in Table 4. Generally the aliphatic amides **10a**, **10b**, **10c**, **10d**, **11a**, **12a**, **13a** and **15a** were obtained in low to moderate yields (entries 1, 2, 3, 4, 7, 9, 10 and 12) whereas attempted preparation of the amides **10e**, **10f**, **11f** and **14a** failed (entries 5, 6, 8 and 11). The reaction conditions (short reaction time, excess of Grignard reagent *versus* acid) led us to apply this method to the synthesis of the corresponding [^{11}C]amides.

Amides labelled with carbon-11

The reaction of carboxylates [^{11}C]-**3** with the amines **4**–**9** was carried out as follows. Cyclotron produced [^{11}C]carbon dioxide was bubbled through a solution of organomagnesium halide **2** in THF or Et_2O at 0 °C for 3 min. [^{11}C]Carbon dioxide was trapped in 80–97% yield. The resulting carboxylate solution was transferred under nitrogen into a second reaction vessel containing the appropriate amine, **4**–**9**, and eventually a further reagent was added (listed in Table 6). The reaction mixture was treated under the conditions described in Tables 5, 6 and 7. The crude product obtained after hydrolysis was analysed by radio TLC and eventually by HPLC. Reactions were always found to lead to a mixture of the desired amides [^{11}C]-**10**–**15** and the carboxylic acids [^{11}C]-**1** resulting from hydrolysis of the unchanged carboxylates [^{11}C]-**3**. Identification of the [^{11}C]carboxylic acids was achieved after their unambiguous synthesis by hydrolysis of the carboxylates [^{11}C]-**3** (Scheme 1). It is noteworthy that [^{11}C]carbon dioxide is always used in very small amounts (< μmol).[13] We can consider that carboxylates [^{11}C]-**3** are present in similar quantities. Usually 0.1–0.5 mmol of alkylmagnesium halides and amines were used respectively to trap [^{11}C]carbon dioxide[17] and to synthesize amides *via* [^{11}C]acid chlorides.[11] Here, the Grignard reagent **2a** and tetrahydroisoquinoline **4** were used in a 10^4 to 10^5 excess over the carboxylate [^{11}C]-**3a** (Table 5). The highest yields were reached when an excess of the amine **4** *versus* the Grignard reagent was used (entry 3) as seen previously (Table 1, entry 9). However, use of the small amount of amine **4** was found to give the amide [^{11}C]-**10a** in a higher purity after HPLC (entry 1).

In our search for reagents useful in amide bond formation, we have investigated the reaction in the presence of Et_3N,[54] 1,8-diazabicyclo[5.4.0]undec-7-ene[54] (DBU) or a pyridine deriv-

Table 3 Reaction of R^1CO_2H **1** with amines **4** or **5** in the presence of a Grignard reagent in THF at 70 °C: yields as a function of time

Entry	R^1CO_2H (mmol)	R^2MgBr (mmol)	Amine (mmol)	Reaction time (min)	Amide	Yields[a] (%)
1	**1a** (2)	**2a** (5)	**4** (2)	5	**10a**	45
				60	**10a**	51
				180	**10a**	54
2	**1a** (2)	**2a** (10)	**4** (2)	5	**10a**	56
3	**1a** (2)	**2b** (5)	**5** (2)	5	**11a**	11
				30	**11a**	37
				180	**11a**	39
4	**1a** (2)	**2b** (10)	**5** (2)	5	**11a**	32
5	**1a** (2)	**2b** (5)	**4** (2)	2	**10b**	8
				5	**10b**	13
				15	**10b**	12.5
6	**1c** (2)	**2b** (5)	**4** (2)	2	**10c**	28
				5	**10c**	22
				30	**10c**	11

[a] Isolated yields.

Table 4 Synthesis of the amides **10**–**15**

Entry	Amine	R^1CO_2MgX	Time (min)	Amide	Yields[a] (%)
1	**4**	**3a**	60	**10a**	65[b]
2		**3b**	5	**10b**	13[c]
3		**3c**	2	**10c**	28[c]
4		**3d**	60	**10d**	28[c]
5		**3e**	60	**10e**	0[c,d]
6		**3f**	60	**10f**	0[c]
7	**5**	**3a**	60	**11a**	39[c]
8		**3f**	60	**11f**	0[c]
9	**6**	**3a**	30	**12a**	37[c]
10	**7**	**3a**	60	**13a**	28.5[d]
11	**8**	**3a**	60	**14a**	0[d]
12	**9**	**3a**	5	**15a**	32[c]

[a] Isolated yields. [b,c,d] Acid/amine/EtMgBr (mmol) respectively 2:5:10, 2:2:5, 2:2:10.

ative[55–59] (Table 6). When the [^{11}C]amidations were carried out in the presence of a pyridinium salt, Et_3N or DBU for 10 min, only a small amount of the expected amide [^{11}C]-**10a** was formed (entries 1, 2, 3 and 4). The reactions carried out in the presence of pyridine or 2,6-di-*tert*-butylpyridine led to the amide [^{11}C]-**10a** in satisfactory yields only if the reaction time was higher than 5 min (entries 5 and 6). The optimum yields were obtained when 2-chloropyridine was employed whatever the reaction time tested (entry 7). However, the improvements in the yields due to the presence of 2-chloropyridine compared to those observed for reactions carried out without any added reagent were not significant (entry 8). Moreover, for ease of purification by HPLC, reactions without 2-chloropyridine were found to be preferable.

The results presented above showed that the amide [^{11}C]-**10a** could be efficiently formed in a reaction time of 10 min and that good yields were already obtained after 1 min (Table 6, entry 8). Because of the half-life of carbon-11, reaction times longer than 10 min were not studied and 5 min was found to be adequate.

Finally, in Table 7 we present the different [^{11}C]amides prepared with this method. In a typical example, the amide [^{11}C]-**10a** was obtained after HPLC purification (Fig. 1) in 25% radiochemical yield (decay corrected to EOB) and in 30 min total synthesis time. Starting from [^{11}C]CO_2 (280 MBq), 20–30 μg of stable amide **10a** was obtained.

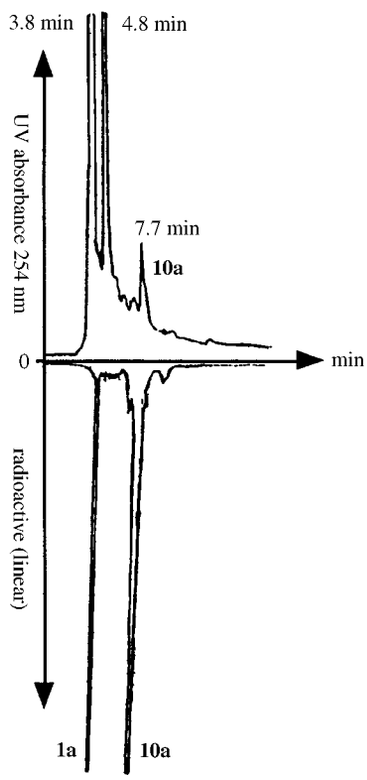


Fig. 1 Preparative HPLC chromatogram of the crude product containing butyric acid [^{11}C]-**1a** and amide [^{11}C]-**10a**

Conclusion

In summary, we have shown that Grignard reagents promoted a rapid reaction of simple carboxylic acids with various aliphatic amines. The conditions required a 2.5 ratio Grignard reagent *versus* acid and THF as the solvent. Aliphatic amides were obtained in moderate to good yields (30–70%) in a short time (5–30 min). The greater the amount of Grignard reagent present, the shorter the reaction time could be, the yields being unchanged.

These conditions were successfully applied to the synthesis of [^{11}C]amides. Reactions of [^{11}C]carboxymagnesium halides yielded the corresponding [^{11}C]amides in 15–60% radiochemical yields (decay corrected to EOB) in 5 min reaction time. This reaction should be considered as a simple method for the synthesis of [^{11}C]amides and presents several advantages. The procedure is extremely easy (it requires only the addition of the amine and no added catalyst). The reaction time is short (5 min). The complete synthesis can be carried out in THF, the solvent generally used to prepare the Grignard reagent.

Work is now in progress to improve yields in aliphatic amides and to prepare aromatic amides by using activated amines both in carbon-11 and stable isotope chemistries.

Experimental

THF was dried by reflux over benzophenone and sodium and distilled under a nitrogen atmosphere. Et_2O was dried by reflux

Table 5 Amide [^{11}C]-**10a**. Yields as a function of PrMgBr **2a** and 1,2,3,4-tetrahydroisoquinoline **4** amounts.

Entry	PrMgBr **2a** (mmol)	Amine **4** (mmol)	Crude yields[a] (%)	Purity[b] (%)
1	0.275	0.0375	52 ± 4	98 ± 2
2	0.275	0.275	38 ± 17	87 ± 13
3	0.275	0.375	63 ± 2	98 ± 2
4	0.0275	0.0375	32 ± 17	75 ± 15

[a] After work-up and before HPLC from the starting carboxylate [^{11}C]-**3a** (decay corrected to EOB, mean values of 2 or 3 runs, reaction in THF for 5 min. [b] Percent of the amide [^{11}C]-**10a** in the crude product determined by radio TLC.

over $LiAlH_4$ and distilled under a nitrogen atmosphere. 1,2,3,4-Tetrahydroisoquinoline was purchased from Aldrich Chem. Co. Inc. and used as received. All other reagents were used as obtained from commercial sources (purity > 98% Janssen Chimica, Aldrich or Sigma). Solutions of organomagnesium halides were prepared from magnesium turnings and alkyl or aryl halides in freshly distilled tetrahydrofuran (THF) or diethyl ether (Et_2O) under nitrogen.[60] They were titrated with menthol in the presence of phenanthroline.[61] IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained from solutions in deuteriochloroform on a Bruker AC-250 spectrometer (250 MHz ^{1}H, 62 MHz ^{13}C) with tetramethylsilane as internal standard. All chemical shifts (δ) are quoted in parts per million. All J values are in Hz. Mass spectra were recorded on a Nermag R10 (EI, 70 eV). Column chromatography was carried out on Silica Gel 60 (70–230 mesh ASTM, Merck). Thin layer chromatography was performed on Silica Gel $60F_{254}$ (0.1 mm, Merck).

[^{11}C]Carbon dioxide was prepared by the ^{14}N (p, α) ^{11}C nuclear reaction using a nitrogen gas target and a baby cyclotron (CGR MeV 325). Bombardment was carried out for 1 min with a 1.5 μA beam of 16 MeV protons. Radioactivity determinations were carried out by a Capintec Radioisotope Calibrator (CRC-12). Identification of the labelled compounds and measures of the radiochemical purities were determined by radio TLC using a Berthold automatic TLC-linear analyser and authentic stable isotope samples as reference. The plates were developed in pentane–ethyl acetate (70:30, eluent A) or in methanol–ethyl acetate (50:50, eluent B). Preparative HPLC was carried out on a Merck HPLC system consisting of intelligent pump (L-6200), UV detector (L-4000), chromato-integrator (D-2500) in series with a scintillation detector (Nardeux). Separations were performed on a reversed-phase column (Waters μ-Bondapak C18, 300 × 7.8 mm) eluted at 3 ml min^{-1} with methanol–water (70:30) at λ = 254 nm.

Preparation of the amides 10–15 from acid chlorides

General procedure. The appropriate acid chloride (0.002 mol) was added dropwise to the amine **4**, **5**, **6**, **7** or **9** (0.002 mol) and triethylamine (0.695 cm^3, 0.005 mol) in dichloromethane (10 cm^3) with stirring under nitrogen. A yellow precipitate was formed immediately. The mixture was refluxed for 60 or 180 min, cooled to room temperature and then washed with aqueous hydrochloric acid (10%; 20–30 cm^3). The mixture was extracted with dichloromethane (2 × 20 cm^3) and the extract dried ($MgSO_4$), filtered and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate–light petroleum as eluent.

***N*-Butyryl-1,2,3,4-tetrahydroisoquinoline 10a.** Purified by chromatography with ethyl acetate–light petroleum (30:70) as eluent to give the pure title compound **10a** (0.406 g, 100%) as a yellow oil, R_f 0.3 (ethyl acetate–light petroleum, 30:70); ν_{max}(NaCl)/cm^{-1} 1652, 1646, 1456 and 1436;[11] δ_H($CDCl_3$) (2 conformers) 0.98 (1H, t, J 7.5, CH_3), 0.99 (2H, t, J 7.5, CH_3), 1.69 (0.7H, sext, J 7.5, CH_3CH_2), 1.71 (1.3H, sext, J 7.5, CH_3CH_2), 2.38 (0.7H, t, J 7.5, CH_2CO), 2.39 (1.3H, t, J 7.9, CH_2CO), 2.87 (2H, m, CH_2Ar), 3.68 (1.3H, t, J 6, CH_2CH_2N), 3.81 (0.7H, t, J 6, CH_2CH_2N), 4.62 (0.7H, s, $ArCH_2N$), 4.73 (1.3H, s, $ArCH_2N$) and 7.12–7.2 (4H, m, C_6H_4); δ_C($CDCl_3$) (2 conformers) 14.1 (CH_3), 18.7 and 18.8 (CH_2CH_2CO), 28.7 and 29.7 (CH_2CO), 35.7 and 35.9 (CH_2CH_2N), 39.7 and 43.3 (CH_2CH_2N), 44.3 and 47.5 ($ArCH_2N$), 126.1, 126.4, 126.5, 126.7, 126.8, 126.9, 128.4, 129.1, 132.8, 133.8, 134.2 and 135.2 (C_6H_4), 172.0 and 172.1 (CO); m/z 203 (M^+, 38%), 132 ($C_9H_{10}N^+$, 36), 104 ($C_8H_8^+$, 51), 91 (37), 77 (100), 71 ($C_4H_7O^+$, 32), 57 (68), 43 ($C_3H_7^+$, 59) and 41 ($C_3H_5^+$, 72).[11]

***N*-Propionyl-1,2,3,4-tetrahydroisoquinoline 10b.** Purified by chromatography with ethyl acetate–light petroleum (30:70) as eluent to give the pure title compound **10b** (0.359 g, 95%) as a yellow oil, R_f 0.3 (ethyl acetate–light petroleum, 30:70); ν_{max}(NaCl)/cm^{-1} 1644, 1434 and 1212;[11] δ_H($CDCl_3$) (2 conformers) 1.12 (3H, t, J 7.4, CH_3), 2.35 (0.6H, q, J 7.4, $COCH_2$), 2.38 (1.4H, q, J 7.4, $COCH_2$), 2.8 (0.6H, t, J 5.9, CH_2CH_2N), 2.82 (1.4H, t, J 5.9, CH_2CH_2N), 3.61 (1.4H, t, J 5.9, CH_2CH_2N), 3.76 (0.6H, t, J 5.9, CH_2CH_2N), 4.54 (1.4H, s, $ArCH_2N$), 4.66 (0.6H, s, $ArCH_2N$) and 7.0–7.15 (4H, m, C_6H_4); δ_C($CDCl_3$) (2 conformers) 9.47 and 9.56 (CH_3), 26.9 and 27.1 (CH_2CO), 28.6 and 29.6 (CH_2CH_2N), 39.7 and 43.2 (CH_2CH_2N or $ArCH_2N$), 44.3 and 47.3 (CH_2CH_2N or $ArCH_2N$), 126.1, 126.4, 126.5, 126.6, 126.7, 126.9, 128.4, 129.1, 132.8, 133.8, 134.2 and 135.2 (C_6H_4) and 172.8 (CO); m/z 189 (M^+, 100%), 174 ($C_{11}H_{12}NO^+$, 60), 117 ($C_9H_9^+$, 28) and 104 ($C_8H_8^+$, 28).[11]

***N*-Acetyl-1,2,3,4-tetrahydroisoquinoline 10c.** Purified by chromatography with ethyl acetate–light petroleum (20:80) as eluent to give the pure title compound **10c** (0.353 g, 95%) as a yellow oil, R_f 0.35 (ethyl acetate–light petroleum, 30:70); ν_{max}(NaCl)/cm^{-1} 1620, 1434, 1250 and 1224; δ_H($CDCl_3$) (2 conformers) 2.18 (1.8H, s, CH_3), 2.19 (1.2H, s, CH_3), 2.85 (1.2H, t, J 6, CH_2CH_2N), 2.91 (0.8H, t, J 6, CH_2CH_2N), 3.68 (1.2H, t, J 6, CH_2N), 3.82 (0.8H, t, J 6, CH_2N), 4.62 (0.8H, s, $ArCH_2N$), 4.73 (1.2H, s, $ArCH_2N$) and 7.12–7.21 (4H, m, C_6H_4);[62] δ_C($CDCl_3$) (2 conformers) 21.7 and 21.9 (CH_3), 28.6 and 29.5 (CH_2CH_2N), 39.7 and 44.1 (CH_2CH_2N or $ArCH_2N$), 44.2 and 48.2 (CH_2CH_2N or $ArCH_2N$), 126.1, 126.5, 126.6, 126.8, 127.1, 127.5, 128.4, 129.6, 132.5, 133.5, 134.1 and 135.2 (C_6H_4), 169.8 and 169.9 (CO); m/z 175 (M^+, 8%), 132 ($C_9H_{10}NO^+$, 19), 117 (24), 104 (33), 77 ($C_6H_5^+$, 42), 63 (17), 51 (36) and 43 ($C_2H_3O^+$, 100).[62,63]

***N*-(2-Methylpropionyl)-1,2,3,4-tetrahydroisoquinoline 10d.** Purified by chromatography with ethyl acetate–light petroleum (85:15) as eluent to give the pure title compound **10d** (0.507 g, 80%) as a yellow oil, R_f 0.65 (ethyl acetate–light petroleum, 85:15); ν_{max}(NaCl)/cm^{-1} 1642 and 1436; δ_H($CDCl_3$) (2 conformers) 1.14 (1.65H, d, J 5.0, CH_3), 1.16 (1.35H, d, J 5.0, CH_3), 2.83 (3H, m, CH_2CH_2N and CH), 3.73 (1.1H, t, J 6.1, CH_2CH_2N), 3.83 (0.9H, t, J 6.1, CH_2CH_2N), 4.67 (0.9H, s, $ArCH_2N$), 4.73 (1.1H, s, $ArCH_2N$) and 7.10–7.21 (4H, m, C_6H_4); δ_C($CDCl_3$) (2 conformers) 19.4 and 19.5 (2 CH_3), 28.5 and 29.9 (CH), 30.6 and 30.8 (CH_2CH_2N), 40.0 and 43.1 (CH_2CH_2N or $ArCH_2N$), 47.4 and 47.9 (CH_2CH_2N or $ArCH_2N$), 126.1, 126.4, 126.5, 126.6, 126.8, 126.9, 128.4, 129.1, 132.9, 133.8, 134.1 and 135.3 (C_6H_4) and 176.0 (CO); m/z 204 (M^+, 45%), 104 (51), 91 (41), 77 (100), 71 (35) and 57 (69).

***N*-Benzoyl-1,2,3,4-tetrahydroisoquinoline 10f.** Purified by chromatography with ethyl acetate–light petroleum (50:50) as eluent to give the pure title compound **10f** (0.436 g, 92%) as a colourless solid (mp 128 °C),[64] R_f 0.8 (ethyl acetate–light petroleum, 50:50); ν_{max}(NaCl)/cm^{-1} 1634, 1446, 1434, 1300, 1288, 1256 and 1236; δ_H($CDCl_3$) (2 conformers) 2.87–2.99 (2H, m, CH_2CH_2N), 3.60–3.71 (1.2H, m, CH_2CH_2N), 3.98–4.08 (0.8H, m, CH_2CH_2N), 4.50–4.68 (0.8H, m, $ArCH_2N$), 4.89–4.98 (1.2H, m, $ArCH_2N$), 7.17–7.20 (4H, m, C_6H_4) and 7.44 (5H, s, C_6H_5);[62] δ_C($CDCl_3$) (2 conformers) 28.4 and 29.7 (CH_2CH_2N), 44.9 and 45.4 (CH_2CH_2N), 49.9 and 53.6 ($ArCH_2N$), 126.7, 127, 128.6, 128.7, 129.0, 129.9, 130.6, 133.1, 134.7 and 136.2 (C_6H_4

Table 6 The amide [^{11}C]-**10a** from the amine **4** (0.375 mmol) and [1-^{11}C]-PrCO$_2$MgBr **3a**:[a] yields as a function of the presence of a potentially activating agent (0.375 mmol)

		Crude yield[b] (%)			Purity[c] (%)		
Entry	Added reagent	1 min	5 min	10 min	1 min	5 min	10 min
1	1-Methyl-2-chloropyridinium iodide	—	—	9 ± 1	—	—	19 ± 2
2	2-Chloropyridinium chloride	—	—	21 ± 2	—	—	98 ± 2
3	Et_3N	—	—	26 ± 1	—	—	99 ± 1
4	DBU	—	—	37 ± 1	—	—	85 ± 13
5	Di-*tert*-butylpyridine	27 ± 1	77 ± 1	65 ± 2	94 ± 2	92 ± 6	90 ± 10
6	Pyridine	47 ± 17	65 ± 2	62 ± 1	80 ± 20	87 ± 5	93 ± 3
7	2-Chloropyridine	64 ± 1	68 ± 1	79 ± 1	95 ± 4	90 ± 2	95 ± 4
8	None	56 ± 3	60 ± 2	76 ± 2	96 ± 1	98 ± 2	96 ± 3

[a] [1-^{11}C]-PrCO$_2$MgBr **3a** was prepared from [^{11}C]-CO$_2$ and PrMgBr (0.275 mmol). [b] After work-up and before HPLC from the starting carboxylate [^{11}C]-**3a** (decay corrected to EOB, mean values of 2 or 3 runs). [c] Percent of the amide [^{11}C]-**10a** in the crude product determined by radio TLC.

Table 7 The synthesis of the amides [^{11}C]-**10**–**12**[a]

Entry	Amine	R^{1}CO$_2$MgX	Amides	Crude yield[b] (%)	Purity[c] (%)
1	**4**	[^{11}C]-**3a**	[^{11}C]-**10a**	52 ± 4	98 ± 2
2		[^{11}C]-**3b**	[^{11}C]-**10b**	40 ± 2	77 ± 5
3		[^{11}C]-**3c**	[^{11}C]-**10c**	68 ± 1	67 ± 2
4		[^{11}C]-**3f**	[^{11}C]-**10f**	23 ± 2	14 ± 2
5	**5**	[^{11}C]-**3a**	[^{11}C]-**11a**	32 ± 2	42 ± 2
6	**6**	[^{11}C]-**3a**	[^{11}C]-**12a**	42 ± 2	45 ± 5

[a] Amine/R^{1}MgX = 0.0375/0.275 (mmol) in THF for 5 min. [b] After work-up and before HPLC from the starting carboxylate [^{11}C]-**3** (decay corrected to EOB, mean values of 2 or 3 runs). [c] Percent of the [^{11}C]-amide in the crude product determined by radio TLC.

and C_6H_5); *m*/*z* 237 (M^+, 77%), 236 ([M − 1]$^+$, 55), 132 ($C_9H_{10}N^+$, 32), 117 ($C_9H_9^+$, 48), 105 ($C_7H_5O^+$, 100) and 104 ($C_8H_8NO^+$, 33).[11,62]

***N*-Butylbutanamide 11a.** Purified by chromatography with ethyl acetate–light petroleum (50:50) as eluent to give the pure title compound **11a** (0.2 g, 70%) as a colourless oil, R_f 0.65 (ethyl acetate–light petroleum, 50:50); ν_{max}(NaCl)/cm^{-1} 1646 and 1264; δ_H($CDCl_3$) 0.85 (3H, t, *J* 7.3, CH_3), 0.87 (3H, t, *J* 7.3, CH_3), 1.18–1.48 (4H, m, C*H*$_2$C*H*$_2$CH$_2$NH), 1.59 (2H, sext, *J* 7.3, C*H*$_2$CH$_2$CO), 2.07 (2H, t, *J* 7.3, CH_2CO), 3.18 (2H, q, *J* 6.6, C*H*$_2$NH) and 5.4 (1H, s, NH); δ_C($CDCl_3$) 13.8 (2 CH_3), 19.3 (*C*H$_2$CH$_2$CO), 20.1 (*C*H$_2$CH$_2$CH$_2$N), 31.8 (*C*H$_2$CH$_2$N), 38.9 (CH_2CO), 39.3 (CH_2N) and 173 (CO).[65]

***N*,*N*-Dipropylbutanamide 12a.** Purified by chromatography with ethyl acetate–light petroleum (50:50) as eluent to give the pure title compound **12a** (0.273 g, 80%) as a colourless oil, R_f 0.65 (ethyl acetate–light petroleum, 50:50); ν_{max}(NaCl)/cm^{-1} 1642, 1464 and 1380; δ_H($CDCl_3$) 0.88 (3H, t, *J* 7.5, CH_3), 0.92 (3H, t, *J* 7.5, CH_3), 0.96 (3H, t, *J* 7.5, CH_3), 1.47–1.72 (6H, m, 3 C*H*$_2$CH$_3$), 2.27 (2H, t, *J* 7.5, CH_2CO) and 3.15–3.30 (4H, m, 2 CH_2N); δ_C($CDCl_3$) 11.3 and 11.5 (2 *C*H$_3$CH$_2$CH$_2$N), 14.1 (*C*H$_3$CH$_2$CH$_2$CO), 19.0 (*C*H$_2$CH$_2$CO), 21.1 and 22.4 (2 *C*H$_2$CH$_2$N), 35.1 (*C*H$_2$CO), 47.5 and 49.7 (2 CH_2N) and 172.7 (CO);[66] *m*/*z* 172 ($M^+ + H^+$, 17.6%), 171 (M^+, 19), 128 ($C_7H_{14}NO^+$, 18.4), 115 (32.5), 114 (37), 101 (82.9), 100 ($C_6H_{14}N^+$, 60.9), 86 ($C_4H_7NO^+ + H^+$, 25.2), 72 (64.9), 71 (19.7) and 45 (100).

***N*-Butyrylmorpholine 13a.** Purified by chromatography with ethyl acetate–light petroleum (50:50) as eluent to give the pure title compound **13a** (0.250 g, 79.6%) as a colourless oil, R_f 0.35 (ethyl acetate–light petroleum, 50:50); ν_{max}(NaCl)/cm^{-1} 1644, 1456, 1436 and 1116; δ_H($CDCl_3$) 0.97 (3H, t, *J* 7.4, CH_3), 1.66 (2H, sext, *J* 7.4, C*H*$_2$CH$_3$), 2.30 (2H, t, *J* 7.4, CH_2CO) and 3.46–3.69 (8H, m, 2 OCH_2CH_2N); δ_C($CDCl_3$) (2 conformers) 13.7 and 14.0 (CH_3), 18.4 and 18.7 (*C*H$_2$CH$_3$), 35.1 and 35.9 (*C*H$_2$CO), 41.9 and 46.1 (CH_2N), 66.7 and 67.0 (CH_2O), 172.0 and 177.6 (CO); *m*/*z* 157 (M^+, 100%), 142 ($C_7H_{12}NO_2^+$, 34) and 129 ($C_6H_{11}NO_2^+$, 56).

Table 8 R_f Values of [^{11}C]carboxylic acids and [^{11}C]amides

		Eluent A	Eluent B
Carboxylic acids	[^{11}C]-**1a**	0.10	0.55
	[^{11}C]-**1b**	0.15	0.40
	[^{11}C]-**1c**	0.10	0.30
	[^{11}C]-**1f**	0.30	0.65
Amides	[^{11}C]-**10a**	0.30	0.80
	[^{11}C]-**10b**	0.20	0.85
	[^{11}C]-**10c**	0.20	0.75
	[^{11}C]-**10f**	0.30	0.90
	[^{11}C]-**11a**	0.75	0.90
	[^{11}C]-**12a**	0.75	0.90

***N*-(Methylbenzyl)butanamide 15a.** Purified by chromatography with ethyl acetate–light petroleum (50:50) as eluent to give the pure title compound **15a** (0.286 g, 75%) as a colourless oil, R_f 0.32 (ethyl acetate–light petroleum, 50:50); ν_{max}(NaCl)/cm^{-1} 1636 and 1540; δ_H($CDCl_3$) 0.92 (3H, t, *J* 7.4, CH_2CH_3), 1.48 (3H, d, *J* 7, $CHCH_3$), 1.68 (2H, sext, *J* 7.4, CH_2CH_3), 2.14 (2H, t, *J* 7.4, CH_2CO), 5.13 (1H, qt, *J* 7, CH_3CH), 5.80 (1H, s, NH) and 7.27–7.33 (5H, m, C_6H_5); δ_C($CDCl_3$) 13.8 (CH_2CH_3), 19.3 (CH_2CH_3), 21.8 (CH_3CH), 38.9 (CH_2CO), 48.6 ($CHCH_3$), 126.3, 127.4, 128.4 and 143.4 (C_6H_5) and 172.1 (CO); *m*/*z* 191 (M^+, 66%), 165 (57), 152 ($C_{12}H_{17}NO^+$, 100), 149 ($C_9H_{10}NO^+$, 62), 109 (65), 105 ($C_8H_9^+$, 67), 77 ($C_6H_5^+$, 65), 71 (43), 55 (42), 43 ($C_3H_7^+$, 97) and 41 ($C_3H_5^+$, 73).

Synthesis of the amides 10–15 from carboxymagnesium halides 3: general procedure

To a solution of alkylmagnesium halide **2** (0.002, 0.003, 0.004, 0.005, 0.01 or 0.015 mol), the carboxylic acid **1** (0.002 mol) was added at 0 °C under nitrogen. After the reaction mixture had been stirred at 70 °C for 15 min, the amine **4**–**9** (0.002, 0.005 or 0.008 mol) was added at 0 °C. The reaction vessel was heated at 70 °C for 2, 5, 30 or 180 min. The mixture was quenched with aqueous hydrochloric acid (10%; 25 cm^3) at 0 °C and extracted with dichloromethane (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel with ethyl acetate–light petroleum as eluent.

Synthesis of carboxylic acids [^{11}C]-1: general procedure

[^{11}C]Carbon dioxide was bubbled at 0 °C for 5 min through a THF or Et_2O (0.1 cm^3) solution of alkylmagnesium halide (1.47 M in THF or Et_2O; 0.2 or 0.02 cm^3). The mixture was then hydrolysed at 0 °C with aqueous ammonium chloride (saturated solution; 1.5 cm^3). The crude reaction mixture was analysed by radio TLC (Table 8).

Synthesis of amides [^{11}C]-10–15: general procedure

To the solution of the carboxymagnesium halide [^{11}C]-**3** in THF prepared as described earlier, the amine **4**–**6** (0.0375, 0.275,

0.375 mmol) was added, followed by the reagent listed in Table 6 (0.375 mmol) and THF (0.2 cm^3). The reaction mixture was heated at 70 °C for 1, 5 or 10 min. After cooling at 0 °C, the mixture was hydrolysed with aqueous hydrochloric acid (2 M; 1 cm^3). The organic and aqueous layers were separated, counted and analysed. Analysis of the organic layer revealed the presence of a mixture of [^{11}C]amide and [^{11}C]carboxylic acid in the ratios shown in Table 7.

Purification of [1′-^{11}C]butyryl-1,2,3,4-tetrahydroisoquinoline 10a

The amide [^{11}C]-**10a** was prepared according to the method described earlier (see above). After hydrolysis with 2 M aqueous hydrochloric acid, the mixture was loaded onto a C_{18} Sep-Pak [pre-wet with methanol (10 cm^3) and then with water (10 cm^3)]. The Sep-Pak was rinsed with water (0.8 cm^3) and dried under nitrogen. The amide [^{11}C]-**10a** was eluted with THF (1.5 cm^3). Solvent was removed from the eluted fractions at 80 °C under nitrogen and after cooling at 0 °C, the radioactive residue was taken up into methanol–water (70:30) and injected *via* a filter (Millipore, Millex-HV_{13}, 0.45 mm, 13 mm) onto an HPLC column. The amide [^{11}C]-**10a** (t_r = 7.70 min; 25.3 MBq; 20–30 μg calculated from a calibration curve in HPLC; >99% radiochemical purity) was collected in 25% yield (decay corrected to EOB starting from 280 MBq of [^{11}C]-CO_2) and within 30 min.

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