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Rapid Room-Temperature ^{11}C-Methylation of Arylamines with [^{11}C]Methyl Iodide Promoted by Solid Inorganic-Bases in DMF

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[^{11}C]Methyl iodide is the most widely used reagent for labeling radiotracers with carbon-11 ($t_{1/2}$ = 20.4 min) for molecular imaging with positron emission tomography. However, some substrates for labeling, especially primary arylamines and pyrroles, are sluggishly reactive towards [^{11}C]methyl iodide. We found that insoluble inorganic bases, especially Li_3N or Li_2O, effectively promote rapid reactions (≤ 10 min) of such substrates with no-carrier-added [^{11}C]methyl iodide in *N*,*N*-dimethylformamide (DMF) at room temperature to give ^{11}C-methylated products in useful radiochemical yields. In particular, we discovered that some primary arylamines in Li_3N/DMF were converted into their corresponding formanilides, and that these were readily *N*-methylated with [^{11}C]methyl iodide, which preceded easy basic hydrolysis to the desired [^{11}C]*N*-methyl secondary arylamines. The use of a solid base permitted selective reaction at an arylamino group and, in some cases, avoided undesirable side reactions, such as ester group hydrolysis. An ultrasound device proved useful to provide remote and constant agitation of the radioactive heterogeneous reaction mixtures but imparted no ultrasound-specific chemical effect.

Introduction

^{11}C-Methylation is an important method to prepare radiotracers for application with positron emission tomography (PET).[1–3] As carbon-11 has a very short half-life of 20.4 min, ^{11}C-methylation procedures must be efficient over short periods, typically less than 10 min.[4,5] [^{11}C]Methyl iodide[6–9] and [^{11}C]methyl triflate[10] are the most accessible and widely used ^{11}C-methylation agents. However, these reagents have some limitations for the ^{11}C-*N*-methylation of arylamines. [^{11}C]Methyl iodide is often poorly effective.[11] The more reactive [^{11}C]methyl triflate can be generated simply by passing [^{11}C]methyl iodide over heated silver triflate[10] and is especially useful for the ^{11}C-methylation of arylamines, where the nucleophilicity of the amino group is reduced by conjugation to the ring.[12,13] However, if the electron density of the aryl group in a primary arylamine is further reduced by an electron-withdrawing group even [^{11}C]methyl triflate may fail to react.

In our program of developing radiotracers for PET imaging, we have encountered several arylamines that show only low or moderate reactivity towards either [^{11}C]methyl iodide or [^{11}C]methyl triflate under conventional heated basic conditions. Moreover, these relatively harsh conditions often lead to the decomposition of substrate and/or product. These amines include precursors for the prospective β-amyloid plaque radioligands, [^{11}C]**1a** and [^{11}C]**1b**, and of a prospective protein kinase C (PKC) receptor radioligand, [^{11}C]**2** (Figure 1).

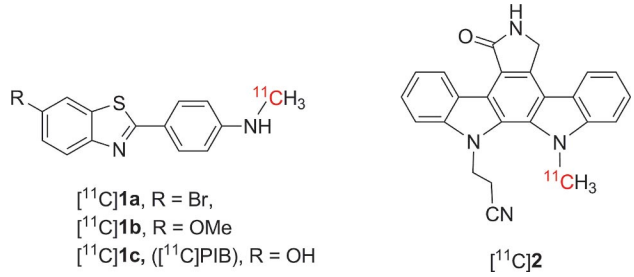

Figure 1. Some known[11] and prospective radiotracers that have sluggishly reactive precursors in labeling reactions with [^{11}C]methyl iodide.

In view of reports that describe the successful use of solid base/solvent combinations to achieve methylation or other alkylation reactions at anilines and pyrroles,[14,15] we decided to explore this approach for the ^{11}C-methylation of such substrates with [^{11}C]methyl iodide. We also aimed to explore ultrasound to achieve constant agitation with the potential to increase reaction yields as documented for several types of organic reactions,[16,17] which include methylation reactions.[18,19] In this study, we found that the use of agitated solid inorganic-bases paired with *N*,*N*-dimethylformamide (DMF) could overcome the sluggish reactivity of arylamines and permit rapid ^{11}C-methylation at room temperature. For certain arylamines, this process was found to occur through unexpected *N*-formyl intermediates.

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Results and Discussion

The aim of this study was to explore the use of solid inorganic-bases to promote rapid reactions of [^{11}C]methyl iodide with primary arylamines and a pyrrole (Figure 1) at room temperature using ultrasound to agitate the heterogeneous reaction mixture. Our major findings were: i) that the use of Li_3N/DMF or Li_2O/DMF provided useful (> 5%) decay-corrected radiochemical yields (RCYs) of ^{11}C-*N*-methylated products, which included unexpected *N*-formyl compounds, ii) that formanilides were themselves useful reactive precursors for the rapid preparation of [^{11}C]-*N*-methylarylamines, and iii) that ultrasound was useful for heterogeneous reaction agitation but did not impart an ultrasound-specific chemical effect.

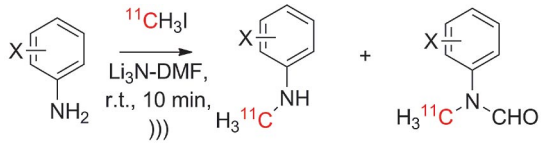
Ultrasound is known to accelerate many types of organic chemical reaction,[16,17] especially those that occur at solid–liquid interfaces.[20,21] Microbubbles formed during the ultrasonication of liquid–solid mixtures may collapse at the phase interface to generate a local temperature of up to 5000 °C within a fraction of a millisecond.[16,22–24] Furthermore, ultrasound between 5 and 24 kHz transfers energy to reactants without dramatically changing the temperature of the bulk medium,[24] which is an attractive feature for reactions that involve compounds with thermally sensitive groups. Despite the widespread use of ultrasound as an energy source in general synthetic organic chemistry, ultrasound has not been considered previously to promote labeling reactions with short-lived isotopes such as carbon-11. In view of the possible advantages, we decided to explore ultrasound for the constant agitation of heterogeneous reaction mixtures and to promote ^{11}C-methylation reactions at sluggishly reactive amino groups.

[^{11}C]Methyl iodide was chosen for this study over the more reactive [^{11}C]methyl triflate to avoid unwanted side reactions. Inorganic bases were selected i) to be strong enough to deprotonate the weakly acidic amino group to be labeled, ii) to have a large lattice energy in the solid form to prevent the base serving as a nucleophile, and iii) to be insoluble in the liquid phase in order to prevent other possible side reactions such as substrate decomposition or direct reaction with [^{11}C]methyl iodide. For the methylation of arylamines, we focused on the use of solid Li_3N, Li_2O, BaO, or KOH as the base. For the ^{11}C-methylation of the pyrrole **12** (Scheme 1), we used solid K_2CO_3.

In the choice of a supporting liquid phase for the reactions, protic solvents and those capable of reacting with strong bases were excluded. Solvents with low water-solubility were avoided so that labeled products could be purified by reverse phase HPLC. Tetrahydrofuran (THF) is known to participate in chemical reactions under strongly basic conditions,[25] and we found that some substrates decomposed extensively in THF within 10 min of ultrasonication (unpublished results). Hexamethylphosphoramide and pyridine were found to give only very low RCYs (< 1%) for reactions of the primary aromatic amines **7a** and **7b** in the presence of Li_3N, and hence their use was not further explored. Therefore, DMF became the liquid phase of choice. We limited all reaction times to 10 min or less to avoid excessive physical decay of carbon-11 during the reaction.

Simple anilines, in particular anilines that carry a *p*-nitro or other electron-withdrawing group, are well-known to be poorly reactive towards alkyl halides, even in the presence of strong bases.[26–29] For example, alkylations of aniline in hydrocarbon solvents promoted by alumina or zeolites take several hours at elevated temperatures.[15] We first tested the ^{11}C-methylation of simple anilines in Li_3N/DMF. *m*-Nitroaniline gave a very low yield (3%) of [^{11}C]*N*-methyl-*m*-nitroaniline ([^{11}C]**4a**, Table 1, Entry 1) whereas *o*- and *p*-nitroaniline gave high (62%) and moderate yields (37%) of the respective [^{11}C]*N*-methyl products, [^{11}C]**4b** and [^{11}C]**4c** (Table 1, Entries 2 and 3). Such reactions might be expected to proceed through deprotonation of the weakly acidic amino group to create a highly nucleophilic anion.[30] However, the RCYs in these reactions appear opposite to the expected rank of basicities and nucleophilicities of the anions (*m*-nitroaniline > *p*-nitro ≈ *o*-nitro). A possible explanation is that the generated concentration of the anion decreased with the increase in the pK_a of the amine for proton loss, although we also note evidence for the *N*-alkylation of weak N–H acids in the presence of a solid base to occur by complex catalytic mechanisms independent of amine deprotonation.[31] Aniline was unexpectedly converted in high RCY (68%) into the ^{11}C-methylated formamide ([^{11}C]**5d**) (Table 1, Entry 4), whereas no labeled formamide derivatives were produced from nitroanilines (Table 1, Entries 1–3). This may suggest that the anion of aniline (aniline pK_a = 30.7)[32] and not any of the anions of the nitroanilines (*p*-nitroaniline pK_a = 20.9)[32] is sufficiently nucleophilic to displace Me_2NH from DMF. DMF has been reported to act as a source of the formyl group in a number of reactions,[33] which include the *N*-formylation of

Table 1. RCYs of labeled products from the reactions of anilines with [^{11}C]methyl iodide in the presence of Li_3N/DMF after ultrasonication for 10 min at room temp.



X =	X =	X =
3a, *m*-NO_2	[^{11}C]**4a**, *m*-NO_2	[^{11}C]**5a**, *m*-NO_2
3b, *o*-NO_2	[^{11}C]**4b**, *o*-NO_2	[^{11}C]5**b**, *o*-NO_2
3c, *p*-NO_2	[^{11}C]**4c**, *p*-NO_2	[^{11}C]**5c**, *p*-NO_2
3d, H	[^{11}C]**4d**, H	[^{11}C]**5d**, H

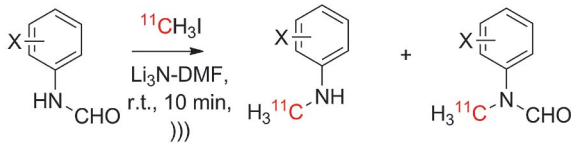
Entry	Precursor	Amine product	RCY[a] [%]	Amide product	RCY [%]
1	**3a**	[^{11}C]**4a**	3	[^{11}C]**5a**	0
2	**3b**	[^{11}C]**4b**	62 ± 3 (59)	[^{11}C]**5b**	0
3	**3c**	[^{11}C]**4c**	37 ± 2 (25)	[^{11}C]**5c**	0
4	**3d**	[^{11}C]**4d**	4	[^{11}C]**5d**	68

[a] Values are mean ± range for n = 2. Values in parentheses are for shaken "silent" reactions.

halo and carboxyl anilines in DMF under reflux in the presence of sodium methoxide.[34]

A low RCY (4%) of [^{11}C]*N*-methylaniline ([^{11}C]**4d**) was coproduced in the reaction of aniline (Table 1, Entry 4). We wondered if this product may have been generated from aniline directly or from the major *N*-formyl product [^{11}C]**5d** during the aqueous quench of the reaction. Accordingly, we tested the influence of the *N*-formyl group on radiolabeling. All the tested formanilides **6a**–**6d** gave aggregate ^{11}C-*N*-methylation (Table 2) in higher yields than the corresponding anilines (**3a**–**3d**, Table 1). The most significant difference arose between *N*-formyl-*m*-nitroaniline (**6a**) and *m*-nitroaniline (**3a**), which gave 45% ^{11}C-methylation with **6a** and only 3% with **3a** (cf. Table 2, Entry 1 with Table 1, Entry 1). For *p*-nitroaniline, no radiolabeled formamide was present after product isolation, probably because of the high reactivity of any formamide towards the LiOH that would have been generated in situ from Li_3N upon quenching with water. Formanilides and *N*-methylformanilides are known to be readily hydrolyzed in alkaline solution and both *N*-methylformanilide (**5d**) and *N*-methyl-*m*-nitroformanilide (**5a**) are much less prone to alkaline hydrolysis than *N*-methyl-*p*-nitroformanilide (**5c**).[35] These facts appear remarkably consistent with our findings in Table 2.

Table 2. RCYs of labeled products from the reactions of simple formanilides with [^{11}C]methyl iodide in the presence of Li_3N/DMF after ultrasonication for 10 min at room temp.



X = **6a**, *m*-NO_2; **6b**, *o*-NO_2; **6c**, *p*-NO_2; **6d**, H

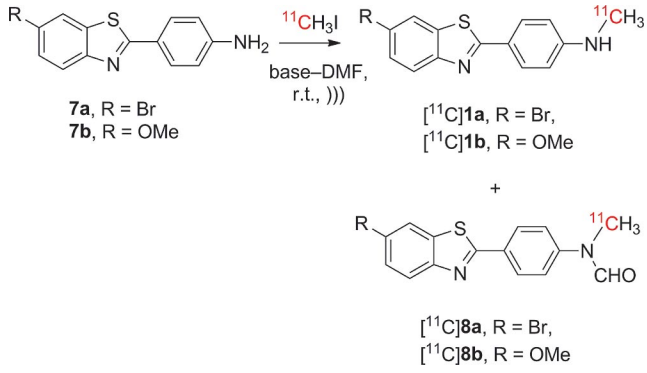
X = [^{11}C]**4a**, *m*-NO_2; [^{11}C]**4b**, *o*-NO_2; [^{11}C]**4c**, *p*-NO_2; [^{11}C]**4d**, H

X = [^{11}C]**5a**, *m*-NO_2; [^{11}C]**5b**, *o*-NO_2; [^{11}C]**5c**, *p*-NO_2; [^{11}C]**5d**, H

Entry	Precursor	Amine product	RCY [%]	Amide product	RCY [%]
1	**6a**	[^{11}C]**4a**	0	[^{11}C]**5a**	45
2	**6b**	[^{11}C]**4b**	20	[^{11}C]**5b**	61
3	**6c**	[^{11}C]**4c**	76	[^{11}C]**5c**	0
4	**6d**	[^{11}C]**4d**	0	[^{11}C]**5d**	77

We are developing prospective radiotracers for imaging brain β-amyloid with PET, such as [^{11}C]**1a** and [^{11}C]**1b**, which are structurally related to the prototypical radiotracer [^{11}C]PIB ([^{11}C]**1c**)[11] (Figure 1). In view of our findings on the ^{11}C-methylation of the simple nitroanilines (Table 1), we were interested to test the same procedure to prepare the structurally more complex targets, [^{11}C]**1a** and [^{11}C]**1b**. For the reaction of the primary arylamine **7a** with [^{11}C]methyl iodide under ultrasonication for 5 min, Li_3N in DMF gave the highest aggregate yield of labeled products (14%), in this case [^{11}C]**1a** as minor product and the *N*-formyl derivative [^{11}C]**8a** as major product (Table 3, Entry 1). An increase in ultrasonication time from 5 to 10 min had a negligible effect on the yield of [^{11}C]**1a** (Entry 2). The closely related arylamine **7b** gave similar yields of the corresponding [^{11}C]*N*-formyl and [^{11}C]*N*-methyl products, [^{11}C]**8b** and [^{11}C]**1b**, respectively, under these conditions (Entry 3). As the major products were [^{11}C]**8a** from **7a** and [^{11}C]**8b** from **7b**, DMF clearly acted as a source of the formyl group as in the reaction of aniline.

Table 3. RCYs of labeled products from the reaction of **7a** and **7b** with [^{11}C]methyl iodide in the presence of solid inorganic-base/DMF under ultrasonication at room temp.



7a, R = Br
7b, R = OMe

[^{11}C]**1a**, R = Br,
[^{11}C]**1b**, R = OMe

[^{11}C]**8a**, R = Br,
[^{11}C]**8b**, R = OMe

Entry	Precursor	Solid base	Time [min]	Amine product	RCY[a] [%]	Amide product	RCY[a] [%]
1	**7a**	Li_3N	5	[^{11}C]**1a**	6	[^{11}C]**8a**	8
2	**7a**	Li_3N	10	[^{11}C]**1a**	6 ± 0.1	[^{11}C]**8a**	9 ± 0.1[b]
3	**7b**	Li_3N	10	[^{11}C]**1b**	4 ± 2 (9)	[^{11}C]**8b**	9 ± 10[c] (2)
4[d]	**7a**	Li_3N	10	[^{11}C]**1a**	3	[^{11}C]**8a**	25
5[d]	**7a**	Li_2O	10	[^{11}C]**1a**	2	[^{11}C]**8a**	22
6[d]	**7b**	Li_2O	10	[^{11}C]**1b**	2	[^{11}C]**8b**	19

[a] Values in parentheses are for shaken reactions. [b] Values are mean ± range for $n = 2$. [c] Mean ± standard deviation for $n = 4$. [d] The precursor and Li_3N/DMF were sonicated for 30 min before [^{11}C]methyl iodide was introduced.

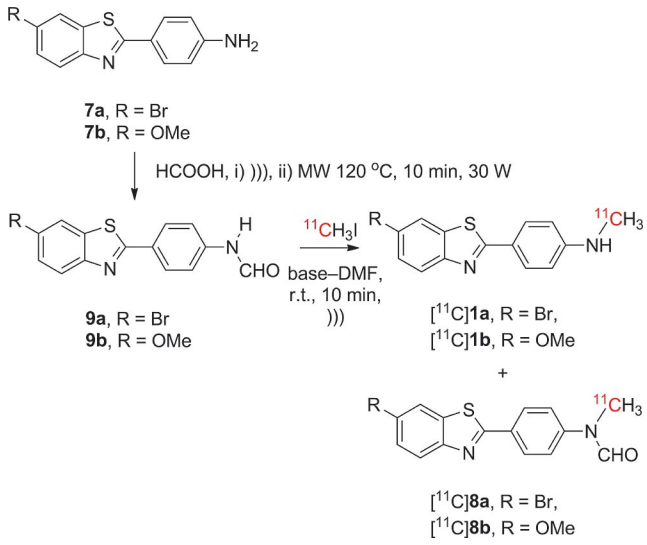
Interestingly, for **7a**, ultrasonication of the reaction mixture for 30 min before the addition of [^{11}C]methyl iodide gave a much higher yield of radiolabeled products (28%), with the [^{11}C]*N*-formyl compound much more prevalent than the [^{11}C]*N*-methyl compound (Table 3, Entry 4). Replacement of Li_3N with Li_2O resulted in similar radioactive product distribution and yields (Entry 5). Arylamine **7b** gave similar results to **7a** under these conditions with the *N*-formyl compound, [^{11}C]**8b**, as the major radioactive product (Entry 6). Our interpretation of these results is that presonication in DMF likely generated substantial concentrations of the formanilides, which reacted more readily than the parent amines with [^{11}C]methyl iodide under basic conditions. Again the reactions likely proceeded through the generation of nucleophilic anions. Consideration of reported pK_a values suggests that anions of formanilide intermediates would be formed much more easily than anions of the parent anilines. Thus, the pK_a of formanilide (19.4)[35] is much lower than that of aniline (30.7),[32] and that of *p*-nitroformanilide (12.5)[36] is much lower than that of *p*-nitroaniline (20.9).[32]

We obtained evidence that the *N*-formyl compounds [^{11}C]**8a** and [^{11}C]**8b** were progenitors of the labeled amines [^{11}C]**1a** and [^{11}C]**1b**, respectively. Thus, after exposure of **7a** and **7b** in DMF to [^{11}C]methyl iodide and ultrasound, we isolated the respective *N*-formyl compounds [^{11}C]**8a** and [^{11}C]**8b** and showed that each was readily hydrolyzed with 1 M KOH at room temperature for 5 min to give the target ^{11}C-*N*-methyl compounds, [^{11}C]**1a** and [^{11}C]**1b**.

Our results and other reports,[37] which describe the ready alkylation of lithium salts of formanilides, prompted us to prepare the formanilides **9a** and **9b** (Table 4) to test their susceptibilities to ^{11}C-*N*-methylation. We found that **7a** and **7b** could be converted into their corresponding non-radioactive formanilides, **9a** and **9b**, with formic acid under microwave irradiation.[38] Ultrasonication of **9a** or **9b** with [^{11}C]methyl iodide in the presence of Li_3N/DMF gave high aggregate yields of labeled products (68 and 50%, respectively), in each case composed of a mixture of the [^{11}C]*N*-methyl derivative with the desformyl analog (Table 4, Entries 1 and 2). Presumably, [^{11}C]**1a** and [^{11}C]**1b** were produced by hydrolysis of the major products [^{11}C]**8a** or [^{11}C]**8b**, respectively. Use of the base/solvent pair KOH/DMF with **9a** or **9b** cleanly gave useful RCYs (66 and 32%) of [^{11}C]**1a** or [^{11}C]**1b** (Entries 3 and 4). These results further emphasize the strong utility of the *N*-formyl group to activate primary arylamines for ^{11}C-*N*-methylation. Importantly, from these results, the ^{11}C-*N*-methylation of formanilides followed by alkaline hydrolysis emerged as a new rapid method to prepare [^{11}C]*N*-methylanilines under mild conditions.

We have explored *p*-aminobenzoic acid esters as prospective radioligands for imaging serotonin subtype-4 receptors with PET.[39] A method to label such compounds with carbon-11 in the *N*-methyl group would be useful. We therefore next attempted the ^{11}C-*N*-methylation of *p*-aminobenzoic acid methyl esters **10a**–**e** in DMF under ultrasonic conditions to assess whether methylation could be achieved without accompanying ester hydrolysis. Li_3N gave no labeled product from methyl *p*-aminobenzoate (**10a**, Table 5, Entry 1), whereas Li_2O gave a modest RCY (15%) of the desired [^{11}C]**11a** (Entry 2). Li_3N also gave extremely low or negligible yields from the aryl ring methoxy-substituted substrates **10b** (Entry 3) and **10c** (Entry 4), whereas Li_2O gave a small yield from **10c** (Entries 5 and 6). The aminobenzodioxan **10d** gave a higher yield (14%) of [^{11}C]**11d** with Li_3N (Entry 7) and no yield with Li_2O (Entry 8). For anilines **10a**–**d** RCYs therefore depended on the steric and electronic features of the aryl ring substituents and their effects on amino group acidity, which may be expected to determine the effective concentration of the nucleophilic anion. A methoxy substituent located *ortho* to the ester group likely prevented the coplanar arrangement of the ester group with the aryl ring, which in turn reduced the electron-withdrawing power of the ester group on the amino group. An electron-donat-

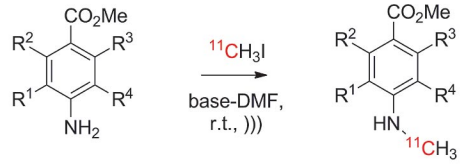
Table 4. RCYs of labeled products from the reaction of **9a** and **9b** with [^{11}C]methyl iodide in the presence of solid inorganic-base/DMF with ultrasonication for 10 min at room temp.



Entry	Precursor	Solid base	Amine product	RCY[a] [%]	Amide product	RCY[a] [%]
1	**9a**	Li_3N	[^{11}C]**1a**	25 (21)	[^{11}C]**8a**	43 (45)
2	**9b**	Li_3N	[^{11}C]**1b**	9 (23)	[^{11}C]**8b**	41 (50)
3	**9a**	KOH	[^{11}C]**1a**	66 (53)	[^{11}C]**8a**	0 (0)
4	**9b**	KOH	[^{11}C]**1b**	32 (35)	[^{11}C]**8b**	0 (0)

[a] Values in parentheses are for shaken "silent" reactions.

Table 5. RCYs of labeled products from the reaction of variously substituted 4-aminobenzoic acid methyl esters with [^{11}C]methyl iodide in the presence of solid inorganic-base/DMF with ultrasonication at room temp.



10a, $R^1 = R^2 = R^3 = R^4 = H$ — [^{11}C]**11a**, $R^1 = R^2 = R^3 = R^4 = H$
10b, R^1 = OMe; $R^2 = R^3 = R^4 = H$ — [^{11}C]**11b**, R^1 = OMe; $R^2 = R^3 = R^4 = H$
10c, $R^1 = R^3 = R^4 = H$; R^2 = OMe — [^{11}C]**11c**, $R^1 = R^3 = R^4 = H$; R^2 = OMe
10d, $R^1 = R^2 = H$; R^3-$R^4 = O(CH_2)_2O$ — [^{11}C]**11d**, $R^1 = R^2 = H$; R^3-$R^4 = O(CH_2)_2O$
10e, R^1 = Cl; $R^2 = R^3 = R^4 = H$ — [^{11}C]**11e**, R^1 = Cl; $R^2 = R^3 = R^4 = H$

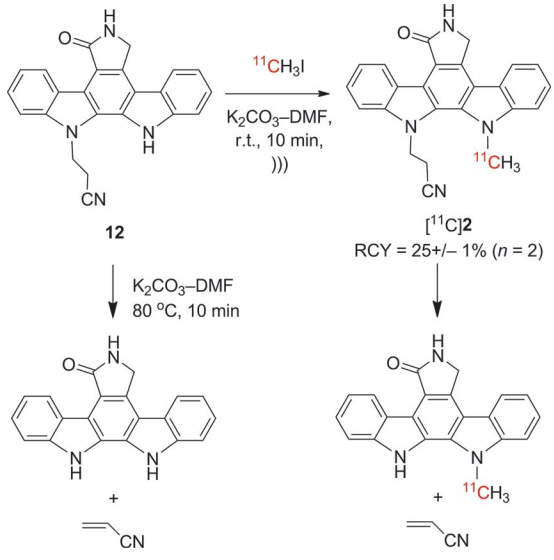
Entry	Precursor	Ring substituent	Solid base	Time [min]	Product	RCY [%]
1	**10a**	None	Li_3N	10	[^{11}C]**11a**	0
2	**10a**	None	Li_2O	10	[^{11}C]**11a**	15 ± 1[a]
3	**10b**	3-MeO	Li_3N	10	[^{11}C]**11b**	4 ± 3
4	**10c**	2-MeO	Li_3N	10	[^{11}C]**11c**	0
5	**10c**	2-MeO	Li_2O	6	[^{11}C]**11c**	6 ± 1[a]
6	**10c**	2-MeO	Li_2O	10	[^{11}C]**11c**	7
7	**10d**	$O(CH_2)_2O$	Li_3N	10	[^{11}C]**11d**	14
8	**10d**	$O(CH_2)_2O$	Li_2O	6–10	[^{11}C]**11d**	0[a]
9	**10e**	3-Cl	Li_2O	2	[^{11}C]**11e**	21 ± 10[a]
10	**10e**	3-Cl	Li_2O	6	[^{11}C]**11e**	31 ± 18[b]
11	**10e**	3-Cl	Li_2O	10	[^{11}C]**11e**	16 ± 13[b]
12	**10e**	3-Cl	BaO	10	[^{11}C]**11e**	8
13	**10e**	3-Cl	Li_3N	12	[^{11}C]**11e**	11

[a] Values are mean ± range for $n = 2$. [b] Mean ± standard deviation for $n > 5$.

ing methoxy group *ortho* to the amino group would also have reduced anion availability. In **10d** both effects operated. By contrast, if a chloro substituent was *ortho* to the amino group, as in **10e**, a useful RCY (up to 31%) of [^{11}C]-**11e** was obtained (Entries 9–11). In Li_2O/DMF the yield of [^{11}C]**11e** was maximal after 6 min of sonication (Entry 10). The specific radioactivity of [^{11}C]**11e** was found to be 6.1 Ci/μmol at the end of radiosynthesis, an acceptably high value for PET applications. BaO and Li_3N gave much lower RCYs (Table 5, Entries 12 and 13, respectively).

Remarkably, no ester hydrolysis was observed for substrates **10a**–**e** under the labeling conditions. The chosen solid inorganic-bases showed selectivity for imparting amino group deprotonation vs. ester hydrolysis. We attribute the lack of nucleophilicity of the bases to their high lattice energies and their insolubility in the reaction solvents.

Pyrrole nitrogen atoms are weakly acidic (e.g. 1*H*-dibenzo[*a*,*i*]carbazole pK_a = 17.7)[30] and recognized to be poorly reactive towards methyl iodide. We were interested to produce the [^{11}C]*N*-methylpyrrole [^{11}C]**2** as a prospective radiotracer to image PKC, by ^{11}C-*N*-methylation of pyrrole **12**.[40] We have previously observed that strong bases eliminate acrylonitrile from **12** (reverse Michael addition, Scheme 1). Even with the weak base K_2CO_3 in the absence of ultrasound but at elevated temperature (80 °C), elimination was complete within 10 min. If an *N*-methyl group was also present, as in **2**, steric crowding further favored elimination under thermal conditions. However, we found that the reaction of **12** with [^{11}C]methyl iodide in DMF/K_2CO_3 with ultrasound at room temperature reduced elimination significantly (Scheme 1). In fact only about 50% of the labeled product underwent elimination, and the target [^{11}C]**2** was obtained in appreciable RCY (25%). This product was obtained with a specific radioactivity of 2.1 Ci/μmol at end of radiosynthesis.



Scheme 1. Labeling of **2** with carbon-11 by treatment of **12** with [^{11}C]methyl iodide in K_2CO_3/DMF for 10 min at room temp. with ultrasonication.

Overall, moderate but useful RCYs of [^{11}C]*N*-methyl compounds were obtained from quite unreactive substrates by brief treatment with ^{11}C-methyl iodide in solid base/DMF at room temperature under the influence of ultrasound. However, we wished to establish whether the ultrasound imparted a specific effect in these reactions other than achieving desired reaction mixture agitation. For this reason, we conducted control reactions in the absence of ultrasound but with occasional shaking to promote uniformity in the heterogeneous reaction mixture. We found that the yields of labeled products in nearly all cases were comparable to those achieved under ultrasonication (Table 1, Entries 2 and 3; Table 3, Entry 3; Table 4, Entries 1–4). This strongly indicates that in this study the major role imparted by ultrasound was mainly limited to constant agitation and promotion of reaction mixture uniformity. Nonetheless, the apparatus employed here proved attractive for this purpose as it can be operated remotely at room temperature and with full radiation safety in a lead-shielded hot-cell.

Conclusions

The use of inorganic base/DMF proved especially effective for the rapid ^{11}C-*N*-methylation of sluggishly reactive arylamines and a pyrrole at room temperature with no-carrier-added [^{11}C]methyl iodide. The bases effectively removed protons at weakly acidic nitrogen atoms and were inactive in the hydrolysis of sensitive benzoic acid esters. Furthermore, this study revealed formanilides to be useful precursors to secondary [^{11}C]*N*-methylarylamines. Additionally, the ultrasound device was found to be a convenient means for heterogeneous radioactive reaction mixture agitation.

Experimental Section

Materials: The following solid inorganic bases were purchased from Aldrich (St. Louis, MO): Li_3N (80 mesh), Li_2O (97%, 60 mesh), BaO (technical grade, 90%, powder), KOH (85% pastilles, crushed in glovebox), and K_2CO_3 (anhydrous powder, crushed in glovebox). DMF was purchased from Alfa Aesar (Ward Hill, MA). *m*-Nitroaniline (**3a**), *o*-nitroaniline (**3b**), *p*-nitroaniline (**3c**), aniline (**3d**), *N*-methyl-3-nitroaniline (**4a**), *N*-methyl-2-nitroaniline (**4b**), *N*-(2-nitrophenyl)formamide (**6b**), *N*-(4-nitrophenyl)-formamide (**6c**), methyl 4-aminobenzoate (**10a**), methyl 4-amino-2-methoxybenzoate (**10c**), methyl 4-amino-3-chlorobenzoate (**10e**), and methyl 4-(methylamino)-3-chlorobenzoate (**11e**) were purchased from Aldrich (St. Louis, MO). *N*-Methyl-4-nitroaniline (**4c**), *N*-(3-nitrophenyl)formamide (**6a**), and methyl 4-(methylamino)-benzoate (**11a**) were obtained from Alfa Aesar (Ward Hill, MA). *N*-Methylaniline (**4d**) was obtained from TCI (Portland, OR). *N*-Methyl-*N*-phenylformamide (**5d**) and *N*-phenylformamide (**6d**) were purchased from Acros (Pittsburgh, PA). Methyl 4-amino-3-methoxybenzoate (**10b**) was purchased from Ryan Scientific (Mt. Pleasant, SC).

General Methods and Instruments: Nonradioactive compounds were analyzed with HPLC with an X-bridge C18 column (5 μm; 10 × 250 mm; Waters Corp., Milford, MA) eluted with aqueous NH_4OH (0.025% v/v)/MeCN at 6.2 mL/min. Eluates were moni-

tored for absorbance at 254 nm (System Gold 168 detector; Beckman, Fullerton, CA). The purity of each compound was expressed as its area percentage of all chromatogram peak areas. ^{1}H NMR (400 MHz) and proton-decoupled ^{13}C NMR (100 MHz) spectra were acquired with an Avance 400 instrument (Bruker, Billerica, MA) using the chemical shifts of residual deuterated solvent as internal standard. Chemical shift (δ) data for the proton and carbon resonances are reported in parts per million (ppm) downfield relative to Me_4Si; s, d, dd, brs, and dm denote singlet, doublet, double doublet, broad singlet, and double multiplet, respectively. LC–MS spectra were acquired with an LCQ^{DECA} instrument (Thermo Fisher Scientific, Waltham, MA) fitted with a Luna C18 column (5 μm; 2.0 × 150 mm; Phenomenex, Torrance, CA) eluted at 150 μL/min with MeOH/H_2O. HRMS were acquired with either electron or electron spray ionization at the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL). An industrial ultrasonic processor instrument (UIS250L, 250 W, 24 kHz; for a description, see: http://downloads.german-pavilion.com/downloads/pdf/exhibitor_19738.pdf), was used to agitate heterogeneous radioactive reaction mixtures in closed vials. These vials (1 mL volume) and their caps were custom-made from inert fluoropolymers. The reaction vial was designed to fit snugly into the port of the instrument so that ultrasound was efficiently transmitted to the reaction mixture. In order to allow reagents to be added and reaction mixtures to be sampled, the septum liner of the vial cap was designed to withstand multiple needle punctures without leaking.

Chemical Syntheses: The following compounds were synthesized as published: 4-(6-bromobenzo[*d*]thiazol-2-yl)-*N*-methylaniline (**1a**),[11] 4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (**1b**),[11] 3-(13-methyl-7-oxo-6,7-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazol-12(13*H*)-yl)propanenitrile (**2**),[41,42] *N*-methyl-4-nitroaniline (**4c**),[43] *N*-methyl-*N*-(3-nitrophenyl)formamide (**5a**),[44] *N*-methyl-*N*-(2-nitrophenyl)formamide (**5b**),[45] *N*-methyl-*N*-(4-nitrophenyl)formamide (**5c**),[44] 4-(6-bromobenzo[*d*]thiazol-2-yl)-aniline (**7a**),[11] 4-(6-methoxybenzo[*d*]thiazol-2-yl)aniline (**7b**),[11] methyl 8-amino-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxylate (**10d**),[45] methyl 3-methoxy-4-(methylamino)benzoate (**11b**),[46–48] methyl 2-methoxy-4-(methylamino)benzoate (**11c**),[46,47] methyl 8-(methylamino)-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxylate (**11d**),[44,45] and 3-(7-oxo-6,7-dihydro-5*H*-indolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazol-12(13*H*)-yl)propanenitrile (**12**).[41,42]

***N*-[4-(6-Bromobenzo[*d*]thiazol-2-yl)phenyl]-*N*-methylformamide (8a):** *N*-Formylarylamine **9a** (20 mg, 0.06 mmol), Li_3N (5 mg, 0.14 mmol), and CH_3I (5 μL, 0.08 mmol) were suspended in DMF (0.5 mL). The suspension was placed in the ultrasonic device, which was set at full power level for half of a 30 min period. The reaction mixture was then quenched with aqueous $HCOONH_4$ (5 M, 0.5 mL). The solvent was evaporated, and the residue was dissolved in DMF. The product **8a** was separated by HPLC (aqueous NH_4OH/MeCN, 49:51 v/v). Purity > 98%; yield 4.2 mg, 20%. ^{1}H NMR ($CDCl_3$): δ = 8.65 (s, 1 H, CHO), 8.12 (dm, $^3J_{HH}$ = 8.6 Hz, 2 H, Ar-H), 8.05 (d, $^4J_{HH}$ = 1.8 Hz, 1 H, Ar-H), 7.92 (d, $^3J_{HH}$ = 8.6 Hz, 1 H, Ar-H), 7.61 (dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 1.9 Hz, 1 H, Ar-H), 7.30 (dm, $^3J_{HH}$ = 8.6 Hz, 2 H, Ar-H), 3.41 (s, 3 H, NCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.1 (CHO), 161.9, 153.0, 144.6, 136.7, 130.9, 130.1, 128.8, 124.3, 124.2, 121.7, 119.0, 31.7 (NCH_3) ppm. MS (TOF): *m*/*z* (%) = 163.0 (5), 350.9 (5), 165.0 (7), 381.2 (13), 349.9 (21), 346.9 (98) $[M + H]^+$. HRMS: calcd. for $C_{15}H_{12}BrN_2OS$ $[M + H]^+$ 346.9854: found 346.9850. Error (ppm): –1.2.

***N*-[4-(6-Methoxybenzo[*d*]thiazol-2-yl)phenyl]-*N*-methylformamide (8b):** The method used to synthesize **8a** was used to prepare **8b** from **9b** (20 mg, 0.07 mmol). The crude product was dissolved in DMF (2.0 mL) and purified by HPLC (aqueous NH_3/MeCN, 73:27 v/v). Purity > 99%; yield 4.8 mg, 23%. ^{1}H NMR ($CDCl_3$): δ = 8.62 (s, 1 H, CHO), 8.09 (dm, $^3J_{HH}$ = 8.8 Hz, 2 H, Ar-H), 7.95 (d, $^3J_{HH}$ = 9.0 Hz, 1 H, Ar-H), 7.37 (d, $^4J_{HH}$ = 2.5 Hz, 1 H, Ar-H), 7.29 (dm, $^3J_{HH}$ = 8.8 Hz, 2 H, Ar-H), 7.11 (dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6 Hz, 1 H, Ar-H), 3.90 (s, 3 H, OCH_3), 3.37 (s, 3 H, NCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 163.8 (CHO), 161.7, 157.7, 148.4, 143.6, 136.2, 131.4, 128.2, 123.5, 121.5, 115.6, 104.0, 55.6 (OCH_3), 31.5 (NCH_3) ppm. MS (TOF): *m*/*z* (%) = 301.1 (8), 300.1 (23), 299.0 (98) $[M + H]^+$. HRMS: calcd. for $C_{16}H_{15}N_2O_2S$ $[M + H]^+$ 299.0854; found 299.0850. Error (ppm): –1.3.

***N*-[4-(6-Bromobenzo[*d*]thiazol-2-yl)phenyl]formamide (9a):** 4-(6-Bromobenzo[*d*]thiazol-2-yl)aniline (**7a**, 20 mg, 0.06 mmol) was dissolved with ultrasonication in formic acid (1.0 mL). The solution was placed in a microwave apparatus (Discover CEM, Matthews, NC) at 120 °C for 10 min using 30 W power and a pressure limit of 200 psi. After the reaction was complete, the solvent was evaporated. The residue was washed with anhydrous diethyl ether to afford crude **9a**, which was dissolved in DMF (2.0 mL) and purified by HPLC (aqueous NH_3/MeCN, 17:83 v/v). Purity > 99%; yield 5.5 mg, 25%. ^{1}H NMR ($CDCl_3$): δ = 10.6 (br. s, 1 H, NH), 8.44 (d, $^3J_{HH}$ = 1.9 Hz, 1 H, CHO), 8.37 (d, $^3J_{HH}$ = 1.6 Hz, 1 H, Ar-H), 8.07 (d, $^3J_{HH}$ = 8.7 Hz, 2 H, Ar-H), 7.96 (d, $^3J_{HH}$ = 8.6 Hz, 1 H, Ar-H), 7.79 (d, $^3J_{HH}$ = 8.7 Hz, 2 H, Ar-H), 7.68 (dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 2.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 167.8 (CHO), 160.1, 152.6, 141.2, 136.3, 129.7, 128.3, 124.8, 124.1, 119.5, 117.8, 117.3 ppm. MS (TOF): *m*/*z* (%) = 336.9 (5), 335.9 (21), 334.9 (98), 332.9 (93) $[M + H]^+$. HRMS: calcd. for $C_{14}H_{10}BrN_2OS$ $[M + H]^+$ 332.9697; found 332.9697. Error (ppm): 0.

***N*-[4-(6-Methoxybenzo[*d*]thiazol-2-yl)phenyl]formamide (9b):** The method used to synthesize **9a** was used with 4-(6-methoxybenzo-[*d*]thiazol-2-yl)aniline (**7b**, 20 mg, 0.07 mmol) to give crude **9b**, which was dissolved in DMF (2.0 mL) and purified by HPLC (aqueous NH_3/MeCN, 13:87 v/v). Purity > 99%; yield 5.3 mg, 24%. ^{1}H NMR (MeOD): δ = 8.66 (s, 1 H, CHO), 8.12 (dm, $^3J_{HH}$ = 8.7 Hz, 2 H, Ar-H), 7.91 (d, $^3J_{HH}$ = 9.0 Hz, 1 H, Ar-H), 7.56 (d, $^4J_{HH}$ = 2.5 Hz, 1 H, Ar-H), 7.49 (dm, $^3J_{HH}$ = 8.7 Hz, 2 H, Ar-H), 7.15 (dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6 Hz, 1 H, Ar-H), 3.92 (s, 3 H, OCH_3) ppm. ^{13}C NMR (CD_3OD): δ = 166.1 (CHO), 164.2, 159.8, 149.5, 145.6, 138.6, 132.6, 129.4, 124.3, 123.2, 117.3, 105.3, 56.4 (OCH_3) ppm. MS (TOF): *m*/*z* (%) = 362.1 (25), 360.1, 324.1 (100), 285.1 (90) $[M + H]^+$. HRMS: calcd. for $C_{15}H_{13}N_2O_2S$ $[M]^+$ 285.0698; found 285.0696. Error (ppm): –0.7.

General Radiochemistry Procedure: No-carrier-added (NCA) [^{11}C]-carbon dioxide was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction by irradiation of nitrogen gas (164 psi) that contained oxygen (1%) with protons (16.5 MeV, 45 μA) generated with a cyclotron (PETtrace 200; GE Healthcare, Milwaukeee, WI). Radiochemistry was performed in lead-shielded hot-cells for radiation protection to personnel. The [^{11}C]carbon dioxide was converted in an automated apparatus (PETrace MeI MicroLab; GE) into [^{11}C]methyl iodide by reduction to [^{11}C]methane followed by a gas-phase reaction with iodine. Within an inert glovebox (oxygen < 10 ppm and moisture < 0.5 ppm), solid inorganic-base (ca. 5 mg), substrate (1.0 mg) and solvent (0.3 mL) were loaded into a fluoropolymer reaction vial (volume 1 mL) and the vial crimp-sealed with a fluoropolymer septum. NCA [^{11}C]methyl iodide (ca. 100 mCi) in nitrogen carrier gas was then bubbled into the reaction mixture. The sealed vial was placed in the port of the ultrasound apparatus (Ultrasonic Processor, UIS250L) and irradiated at full power for 50% of the time, unless otherwise indicated, for a set period (≤ 10 min). The reac-

tion mixture was filtered through a celite plug to obtain a clear solution (syntheses of [^{11}C]**11a**–**11e** only) or quenched by the addition of water (0.5 mL). The radioactive product was then separated by reverse phase HPLC eluted with 0.1 M $HCOONH_4$/MeCN, with eluate monitored for radioactivity and absorbance, as detailed below. The identities of labeled products were confirmed chromatographically by observation of coelution with nonradioactive reference compounds in HPLC and/or by LC–MS of the associated carrier. Decay-corrected RCYs of measured isolated radioactive product were calculated from the amount of [^{11}C]methyl iodide added to the reaction vial. The specific radioactivities (Ci/μmol) of some products were calculated by measurement of the mass of carrier with calibrated analytical HPLC through absorbance detection and measurement of the associated radioactivity. Some reactions were performed with ultrasound irradiation before addition of [^{11}C] methyl iodide. Some control reactions were performed without ultrasound irradiation, but with shaking at 0, 5 and 10 min. Thus, were prepared:

[^{11}C]4-(6-Bromobenzo[*d*]thiazol-2-yl)-*N*-methylaniline ([^{11}C]1a): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (3:7 v/v) at 6.2 mL/min (λ = 350 nm) (t_R = 13.0 min).

[^{11}C]4-(6-Methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline ([^{11}C]1b): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (2:3 v/v) at 6.2 mL/min (λ = 350 nm) (t_R = 10.0 min).

[^{11}C]3-[13-Methyl-7-oxo-6,7-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazol-12(13*H*)-yl]propanenitrile ([^{11}C]2): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (9:11 v/v) at 6.2 mL/min (λ = 292 nm) (t_R = 7.5 min); elimination side product (t_R = 8.3 min).

[^{11}C]*N*-Methyl-3-nitroaniline ([^{11}C]4a): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (3:2 v/v) at 6.2 mL/min (λ = 254 nm) (t_R = 13.2 min).

[^{11}C]*N*-Methyl-2-nitroaniline ([^{11}C]4b): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (1:3 v/v) at 6.2 mL/min (λ = 254 nm) (t_R = 6.1 min) or on the same column eluted at 6.2 mL/min with a gradient of $HCOONH_4$/MeCN (30% MeCN for 1 min increased linearly to 50% MeCN at 30 min) (λ = 254 nm) (t_R = 21.4 min).

[^{11}C]*N*-Methyl-4-nitroaniline ([^{11}C]4c): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (3:2 v/v) at 6.2 mL/min (λ = 254 nm) (t_R = 9.4 min) or on the same column eluted at 6.2 mL/min with a gradient of $HCOONH_4$/MeCN (30% MeCN for 1 min increased linearly to 50% MeCN at 30 min) (λ = 254 nm) (t_R = 12.6 min).

[^{11}C]*N*-Methylaniline ([^{11}C]4d): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted at 6.2 mL/min with a gradient of $HCOONH_4$/MeCN (30% MeCN for 1 min increased linearly to 50% MeCN at 30 min) (λ = 254 nm) (t_R = 13.3 min).

[^{11}C]*N*-Methyl-*N*-(3-nitrophenyl)formamide ([^{11}C]5a): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted at 6.2 mL/min with a gradient of $HCOONH_4$/MeCN (30% MeCN for 1 min increased linearly to 50% MeCN at 30 min) (λ = 254 nm) (t_R = 7.3 min).

[^{11}C]*N*-Methyl-*N*-(2-nitrophenyl)formamide ([^{11}C]5b): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted at 6.2 mL/min with a gradient of $HCOONH_4$/MeCN (30% MeCN for 1 min increased linearly to 50% MeCN at 30 min) (λ = 254 nm) (t_R = 8.1 min).

[^{11}C]*N*-Methyl-*N*-phenylformamide ([^{11}C]5d): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with gradient of $HCOONH_4$/MeCN (30% MeCN for 1 min increased linearly to 50% MeCN at 30 min, v/v) at 6.2 mL/min (λ = 254 nm) (t_R = 7.8 min).

[^{11}C]*N*-[4-(6-Bromobenzo[*d*]thiazol-2-yl)phenyl]-*N*-methylformamide ([^{11}C]8a): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (3:7 v/v) at 6.2 mL/min (λ = 350 nm) (t_R = 8.7 min).

[^{11}C]*N*-[4-(6-Methoxybenzo[*d*]thiazol-2-yl)phenyl]-*N*-methylformamide ([^{11}C]8b): HPLC isolation: Luna C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (2:3 v/v) at 6.2 mL/min (λ = 350 nm) (t_R = 7.0 min).

[^{11}C]Methyl 4-(Methylamino)benzoate ([^{11}C]11a): HPLC isolation: Gemini-NX C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (1:1 v/v) at 6 mL/min (λ = 254 nm) (t_R = 5.4 min).

[^{11}C]Methyl 3-Methoxy-4-(methylamino)benzoate ([^{11}C]11b): HPLC isolation: Gemini-NX C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (1:1 v/v) at 6 mL/min (λ = 254 nm) (t_R = 6.7 min).

[^{11}C]Methyl 2-Methoxy-4-(methylamino)benzoate ([^{11}C]11c): HPLC isolation: Gemini-NX C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (3:2 v/v) at 4 mL/min (λ = 254 nm) (t_R = 7.4 min).

[^{11}C]Methyl 8-(Methylamino)-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxylate ([^{11}C]11d): HPLC isolation: Gemini-NX C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (3:2 v/v) at 5 mL/min (λ = 254 nm) (t_R = 7.6 min).

[^{11}C]Methyl 3-Chloro-4-(methylamino)benzoate ([^{11}C]11e): HPLC isolation: Gemini-NX C18 column (5 μm, 10 × 250 mm) eluted with $HCOONH_4$/MeCN (1:1 v/v) at 6 mL/min (λ = 254 nm) (t_R = 9.5 min).

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