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Synthesis of ^{11}C-epoxides, aziridines, and cyclopropanes from structurally modified ^{11}C-sulfur ylides

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A method for the radiosynthesis of ^{11}C-epoxides, aziridines, and cyclopropanes is described. Through generating ^{11}C-methyl sulfonium salts and corresponding sulfur ylides, the formation of ^{11}C-epoxides is possible in moderate-to-high radiochemical conversions. This method is translated to other 3-membered cyclic species and drug-like scaffolds. Automated radiosynthesis with this method suggests viability for clinical PET radiochemistry.

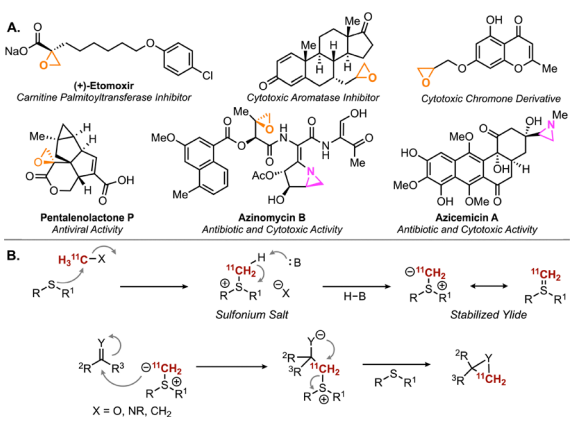
Positron emission tomography (PET) is a non-invasive imaging technique that enables the *in vivo* imaging of biological processes to probe disease states. The production of PET radiotracers involves the incorporation of unnatural β^+-emitting isotopes into a molecule of interest. Frequently, small molecule PET tracers are labelled with ^{11}C or ^{18}F given these isotopes' simple production on commercial cyclotrons and the prevalence of carbon and fluorine in drug-like molecules.

^{11}C-Methylating reagents like [^{11}C]CH_3I and [^{11}C]CH_3OTf have found widespread use in clinical PET tracer production as means to radiolabel nucleophilic functionalities through displacement (O, N, S) and cross-coupling reactions.[1] Despite the commonality and operational simplicity of ^{11}C-methylations, [^{11}C]CH_3X synthons otherwise generate limited chemical diversity. To maximize the utility and chemical diversity available from [^{11}C]CH_3X reagents, we sought novel methods for their incorporation into chemical scaffolds.

We aimed to utilize [^{11}C]CH_3I or [^{11}C]CH_3OTf with sulfide nucleophiles to form radiolabelled sulfonium salts and generate their sulfur ylides for novel radiolabelling, similar to previously explored ^{11}C-phosphonium salts.[2] Sulfur ylides are versatile reagents in cycloadditions, cross couplings, rearrangements, annulations, and carbene precursors.[3–6]

Given the prevalence of epoxides in drug molecules (Scheme 1A), we were initially interested in whether transformation of a ^{11}C-sulfonium salt to the corresponding ylide, in the presence of a suitable carbonyl compound, would enable a Johnson–Corey–Chaykovsky-type reaction to form ^{11}C-epoxides (Scheme 1B) as ubiquitous intermediates for synthesis and bioactive motifs. Further, we aimed to extend the use of these non-stabilised ylides to imines and activated alkenes to label medicinally valuable aziridines and cyclopropanes.[7,8] We believed that a method for the generation of the ^{11}C-isotopologues of these functionalities would serve as a valuable tool for radiochemistry, particularly in cases where ^{11}C-methylation of a target molecule may not be feasible.

The trimethyl sulfonium ($Me_3S^+I^-$) and sulfoxonium iodide ($Me_3SO^+I^-$) reagents typically employed in analogous cycloadditions provide no selectivity in the group transferred. Correspondingly, the generation of the equivalent ^{11}C-reagent would result in undesirable isotopic dilution and low molar activities of the desired ^{11}C-products. This, combined with the short half-life of ^{11}C ($t_{1/2}$ = 20.4 min), motivated an alternative approach for translation to radiochemistry. To ensure the exclusive



Scheme 1 (A) Bioactive compounds featuring epoxide and aziridine motifs. (B) Formation of ^{11}C-epoxides *via* sulfonium salts.

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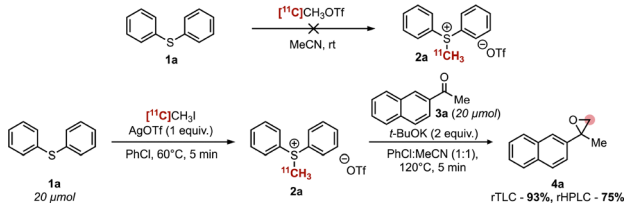


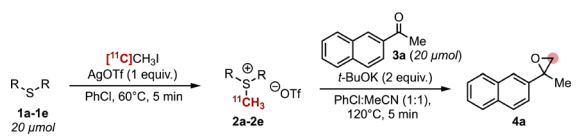
Scheme 2 [^{11}C]MeOTf and [^{11}C]MeI in formation of sulfonium salt **2a**.

transfer of the ^{11}C–CH_3 group, we attempted to synthesise the biaryl sulfonium salt **2a** (Scheme 2). We began by exposing sulfide **1a** to [^{11}C]CH_3OTf at ambient temperature, however this produced multiple products and was not viable in an attempted ^{11}C-epoxide formation. We reasoned that the high reactivity of pure [^{11}C]CH_3OTf dissuades direct product formation by promoting favourable side reactions including solvolysis from residual H_2O and potential reactivity with MeCN leading to further reactive intermediate formation.[9]

We believed that the introduction of AgOTf could aid in product formation through the slow generation of [^{11}C]CH_3OTf from less reactive [^{11}C]CH_3I. Screening conditions with [^{11}C]CH_3I in the presence of AgOTf and **1a** successfully produced the desired sulfonium salt at 60 °C over 5 minutes in PhCl. Application of the formed sulfonium salt **2a** to the synthesis of **4a** produced the desired epoxide in good radiochemical conversion (RCC) when using KO*t*Bu at 120 °C over 5 minutes.

We next examined the effect the sulfonium salt and its respective ylide species had on epoxidation (Table 1). Exposing sulfides **1a–1e** to identical conditions in the formation of **2a**, we compared their conversion to **4a**. While all the sulfides formed their sulfonium salts equally effectively by rTLC, they differed significantly in conversion to **4a**. The biaryl sulfides **1a–1c** (Table 1, entries 1–3) showed a preference for electron dense aryl substituents with **2b** performing most effectively, while tricyclic sulfides **1d** and **1e** (Table 1, entries 4 and 5) were substantially less effective in the formation of **4a**. In all, this suggests that the rigidity and electron density of the operant sulfur ylide influence the nucleophilicity toward attack on the carbonyl of **3a**.

Table 1 Conditions-[^{11}C]CH_3I (in PhCl) added to **1a–e** (20 μmol) and AgOTf (1 eq.) (300 μL PhCl), heated to 60 °C for 5 min to form **2a–e**; 200 μL of **2a–e** solution added to vial containing KOtBu (2 eq.), treated with **3a** (20 μmol, 200 μL MeCN) and stirred at 120 °C for 5 min before filtering and rHPLC analysis



Entry	Sulfide	**4a** (rTLC) (%)	**4a** (rHPLC) (%)
1	**1a**	93	75
2	**1b**	**92**	**86**
3	**1c**	87	60
4	**1d**	77	42
5	**1e**	65	21

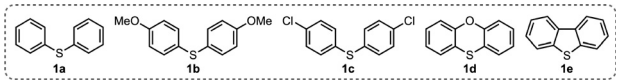
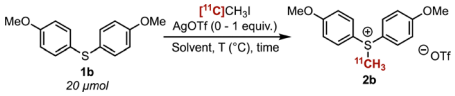


Table 2 Investigation of **2b** formation conditions

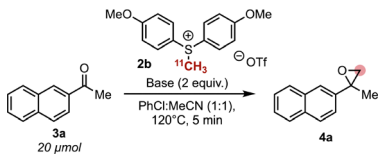


Entry	Solvent	*T* (°C)	AgOTf	Time	**2b** (rHPLC)
1	MeCN	80	1.0 eq.	15 min	Trace
2	PhCl	120	0 eq.	5 min	Trace
3	PhCl	60	1.0 eq.	5 min	91%
4	PhCl	rt	1.0 eq.	5 min	25%
5	PhCl	60	0.75 eq.	5 min	89%
6	PhCl	60	0.5 eq.	5 min	56%

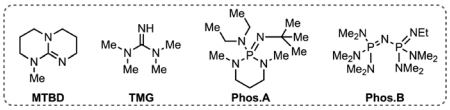
Due to the electron rich nature of the most successful sulfide **1b**, we investigated the synthesis of its respective sulfonium salt **2b** under milder conditions (Table 2). While this revealed that the AgOTf loading could be modestly reduced without detriment, attempts to form **2b** in the absence of AgOTf, even at 120 °C, were unsuccessful. Furthermore, MeCN was not a compatible solvent for **2b** formation.

We proceeded to explore the range of bases that could be employed alongside **2b** to form the operant ylide species (Table 3). The pK_a of **2b** is unknown, though similar sulfonium species display pK_as 16–18, prompting us to explore strong organic and inorganic bases.[10] KO*t*Bu provided improved RCC to **4a** over KOH, and comparable results at lower equivalency (Table 3, entries 1–3). Reducing the temperature of the reaction to 80 °C gave a similar result to 120 °C for **4a** (Table 3, entry 4), however significantly reduced RCCs were noticed with substrates **4b** and **4g** at 80 °C (*vide infra*). Phosphazene bases successfully promoted the reaction with P_2-Et similarly effective to KOH

Table 3 Conditions-[^{11}C]CH_3I (in PhCl) added to **1b** (20 μmol) and AgOTf (1 eq.) (300 μL PhCl), heated to 60 °C for 5 min to form **2b**; 200 μL of **2b** solution added to vial containing base (2 eq.), treated with **3a** (20 μmol, 200 μL MeCN) and stirred at 120 °C for 5 min before filtering and rHPLC analysis



Entry	Base	**4a** (rTLC)	**4a** (rHPLC)
1	KOH (*n* = 3)	78% (± 11%)	64% (±13%)
2	***t*-BuOK (*n* = 3)**	**92%** (±<**1%**)	**82%** (±**11%**)
3	*t*-BuOK (1 eq., *n* = 3)	85% (±2%)	65% (±10%)
4[a]	*t*-BuOK (1 eq., *n* = 1)	91%	77%
5	MTBD	3%	0%
6	TMG	6%	0%
7	Phos.A	40%	11%
8	P_2-Et (Phos.B)	53%	58%



[a] At 80 °C.

though alternative organic bases were ineffective (Table 3, entries 5–8) perhaps on account of their hygroscopicity.

Applying the optimized protocol to a range of substrates featuring aldehydes and ketones, we discovered that those featuring electron withdrawing or neutral substituents performed well (**4b**, **4c**, **4e**, **4g**, **4h**) with aldehyde substrates requiring only 1 equivalent of KOtBu to give high conversions (Fig. 1). **4d** unfortunately only gave complex mixtures which can be attributed to the known instability of electron-rich epoxides and their propensity to form polymers.[11] Heterocyclic examples **4i** and **4j** were formed in modest RCC, as were spirocyclic epoxides **4k** and **4l**. Further, example **4f** and its precursor **3f** feature a competing acidic benzylic site which was tolerated in low RCCs.

Substrates **4b** and **4g** feature ester groups which may be subject to transesterification in the presence of potassium *tert*-butoxide. This prompted us to change to the non-nucleophilic P_2-Et as an alternative, affording both epoxides in good RCCs.

To complement the synthesis of ^{11}C-epoxides, we aimed to expand this protocol to other valuable functionalities accessible from sulfur ylides including aziridines and cyclopropanes. Electron rich aziridine **4m** was challenging with only low RCCs achieved regardless of temperature or base employed, however N-Ts aziridine **4n** could be formed in fair RCCs albeit with notable variability.

Extension of the protocol to activated alkenes was also feasible, with **4o** formed successfully in moderate RCC. Notably, the trifluoromethyl substituted cyclopropane present in **4o** can be employed as a replacement for metabolically labile *tert*-butyl groups in medicinal compounds.[8]

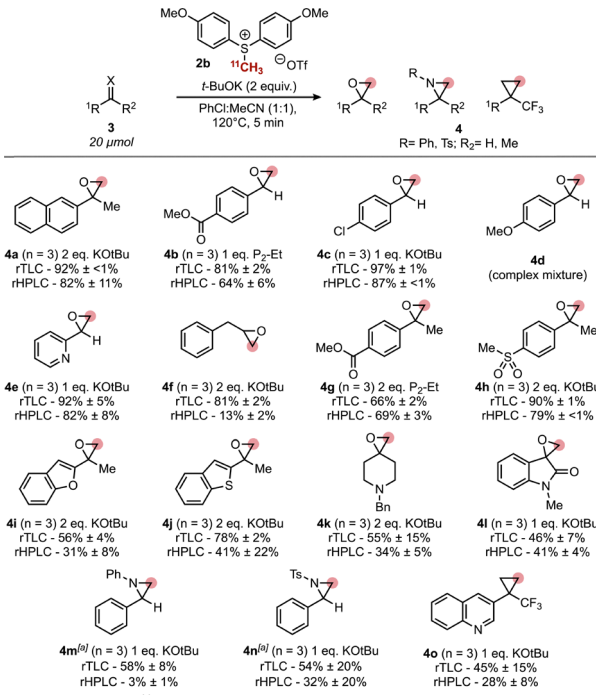


Fig. 1 Conditions-[^{11}C]CH_3I (in PhCl) added to **1b** (20 μmol) and AgOTf (1 eq.) (300 μL PhCl), heated to 60 °C for 5 min to form **2b**; 200 μL of **2b** solution added to vial containing base, treated with **3a–o** (20 μmol, 200 μL MeCN) and stirred at 120 °C for 5 min before filtering and rHPLC analysis. [a] Reaction performed at 100 °C.

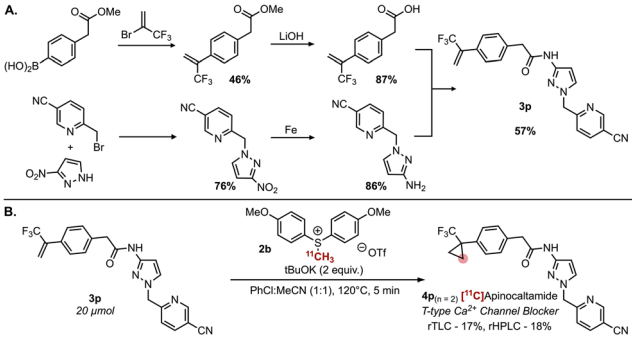


Fig. 2 (A) Synthesis of precursor **3p**. (B) Radiosynthesis of [^{11}C]Apinocaltamide **4p**.

Further, we wanted to examine this method in the context of biologically active, complex substrates as a feasible means to clinically relevant ^{11}C-products. The successful synthesis of **4o** prompted us to attempt the synthesis of the T-type calcium channel blocker [^{11}C]apinocaltamide (ACT-709478) **4p** using alkene precursor **3p** which was accessed in 5 steps from commercially available starting materials in high yields (Fig. 2A). Subsequently, we managed to successfully form **4p** in modest RCC (Fig. 2B), following our standard conditions with 2 equivalents of KOtBu.

Apart from being privileged motifs in select bioactive molecules, epoxides can be versatile intermediates for further chemical differentiation.[12] To illustrate this, we attempted a ring-opening hydrolysis of **4a** (Fig. 3). Transformation of epoxide **4a** to diol **5** was achieved by introducing H_2O and TFA after completion of the epoxide formation. This transformation confirms the presence of epoxide **4a** as an intermediate product and provides a novel route to radiolabelled diols.

Using [^{11}C]CH_3OTf in the formation of our sulfonium salts would simplify the reaction protocol and avoid the addition of silver. We therefore reinvestigated the use of [^{11}C]CH_3OTf with aliphatic cyclic sulfide **1f** in effort to prevent any possible side reactions (Scheme 3). We first subjected **1f** to [^{11}C]CH_3I using our standard conditions, successfully forming **2f** and proceeding to form epoxide **4b** in modest RCC. Unfortunately, while the analogous formation of **2f** using [^{11}C]CH_3OTf appeared successful by rTLC, rHPLC revealed a much broader peak than expected for **2f** and, although subsequent formation of epoxide **4b** was possible, the RCC was very low. The reasons for differing results when using [^{11}C]CH_3OTf and [^{11}C]CH_3I are likely a result of intractable byproduct formation from highly reactive [^{11}C]CH_3OTf the identity of which remain unclear and need to be further investigated in the future.[9]

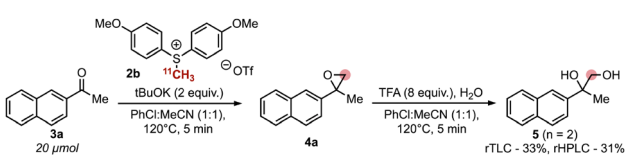
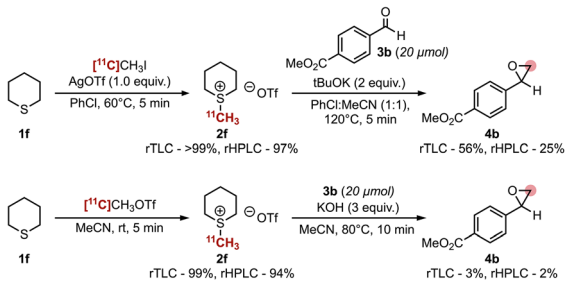


Fig. 3 Radiolabelling of diol **5** from hydrolysis of epoxide **4a**.



Scheme 3 Reactivity of sulfide **2f** formed using $[^{11}C]CH_3I$ or $[^{11}C]CH_3OTf$.

Finally, we attempted an automated procedure using higher activities of $[^{11}C]CH_3I$ (>500 mCi) adapted from the manual conditions. Automation of the method provided a set of challenges relative to the manual reactions. The formation **2b** from $[^{11}C]CH_3I$ proceeded successfully, however it was not fully consumed in the second step unless the amount of P_2-Et base was increased relative to the manual reactions with **3b**. Additionally, the subsequent step at 120 °C produced a new major signal by rHPLC, which had been observed only as a minor byproduct previously, with only trace **4b** observed. Lowering the temperature of the reaction allowed us to favour epoxide formation over byproduct, suggesting both significant differences between the manual and automated heating efficiencies and the thermal instability of **4b**. Nevertheless, with modified conditions, we successfully isolated 22 mCi of **4b** in 99% radiochemical purity from 600 mCi of $[^{11}C]CH_3I$ (3.65% non-decay corrected activity yield) in 19 minutes with a molar activity >710 mCi μmol^{-1} (n = 2). Analysis of the crude reactions showed only a modest decrease in RCC relative to the manual reactions (59%).

In summary, we have produced a range of radiolabelled sulfonium salts, formed their respective sulfur ylides, and explored their reactivity under conditions amenable to ^{11}C-radiolabelling. Synthesis of simple and complex (hetero)aryl epoxides from aldehydes and ketones has been explored and extension of the protocol to the formation of aziridines and trifluoromethyl substituted cyclopropanes was also accomplished. The process can be automated using a radiochemistry synthesis module and is amenable for the ^{11}C-labelling of biologically active, complex substrates that are relevant for clinical PET imaging applications (Scheme 4).

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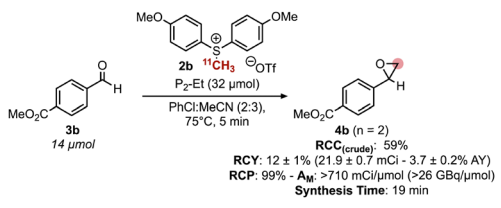

Scheme 4 Automated radiosynthesis of **4b** from aldehyde **3b**.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data supporting this article are all available in the supplementary information (SI). Supplementary information: experimental/synthetic protocols, characterization data, radioTLC and HPLC traces. See DOI: https://doi.org/10.1039/d5cc05951h.

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