Interrupted Aza-Wittig Reactions Using Iminophosphoranes to Synthesize ^{11}C-Carbonyls

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Abstract

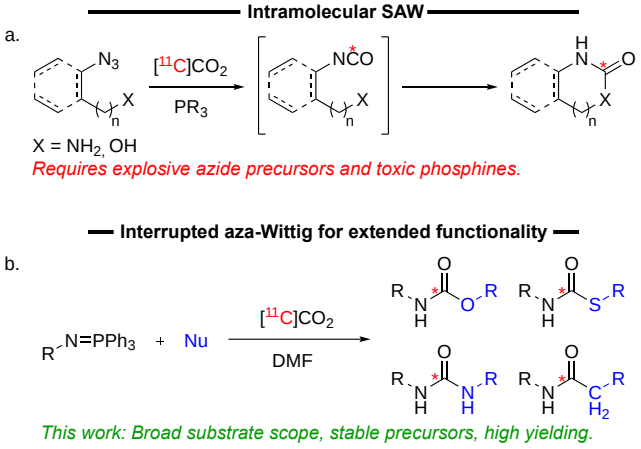
Carbonyls are frequently found in bioactive compounds due to their propensity for hydrogen bonding and synthetic utility in functional group manipulations. Carbon-11 (^{11}C) is routinely incorporated into small molecule radiotracers for positron emission tomography (PET) imaging. Herein, we report a high-yielding, direct CO_2-fixation methodology coupling structurally diverse iminophosphoranes with various nucleophiles to synthesize ureas, carbamates, thiocarbamates, and amides, and which is amenable for ^{11}C radiolabeling. The success of this strategy relies upon the interception of an isocyanate intermediate of sequential aza-Wittig reactions using a suitable nucleophile. This methodology is practical, as demonstrated by the synthesis of >35 products and isolation of the radiopharmaceuticals [^{11}C]URB694 (13% radiochemical yield, 69 GBq·μmol^{-1}) and [^{11}C]glibenclamide (62% RCY, 59 GBq·μmol^{-1}), within 17 minutes and 21 minutes from [^{11}C]CO_2, respectively.

Introduction

Positron emission tomography (PET) is a non-invasive molecular imaging modality used to evaluate biological processes *in vivo* with short-lived radionuclides. PET radiopharmaceuticals are used to diagnose metastatic and cardiovascular diseases, conduct non-invasive pathology studies to detect biomarkers of neurodegeneration, and to probe molecular and functional mechanisms in living systems.[1] Carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min) is prized for isotopic labeling of biomolecules and pharmaceuticals, and is routinely incorporated into PET imaging agents for both research and clinical applications.[2,3] Currently, a lack of diverse methods for directly incorporating [^{11}C]CO_2 into complex molecules has limited its use.[4] Consequently, [^{11}C]CO_2 is most often converted into reactive secondary precursors such as [^{11}C]CH_3I or [^{11}C]CH_3OTf, which are accompanied by elongated processing times and significant reductions in radiochemical yield due

to sub-quantitative conversions.[5–8] Isocyanates are valuable synthetic intermediates that can be readily converted into pharmaceutically-relevant functional groups such as carbamates, ureas, and amides.[9,10] Conventional approaches to synthesizing ^{11}C-isocyanates rely on stepwise trapping of [^{11}C]CO_2 with amines, followed by dehydration using phosphoryl chloride ($POCl_3$) or Mitsunobu-type conditions.[4,11,12] Importantly, the former strategy displays poor tolerance towards anilines and the highly acidic conditions pose challenges for maintaining efficient trapping of [^{11}C]CO_2 in solution. The latter technique has displayed improved utility for synthesizing asymmetrical ureas[12] and also amides using either Grignard reagents[13] or organozinc coupling reactions,[14] though high mass loading of azo reagents and phosphines may complicate radiotracer purification. Each strategy requires careful control of temperature and reagent concentrations during sequential reaction steps in order to prevent formation of complex mixtures of symmetrical byproducts and heterocycles.[11,15] Iminophosphoranes have been shown to undergo the aza-Wittig reaction directly with CO_2 to produce isocyanates in high yields.[16] Indeed, similar reactivity towards carbonyl containing functional groups has been exploited in the synthesis of complex alkaloids such as (-)-dendrobine and a myriad heterocyclic drugs and natural products.[17,18] In the context of ^{11}C, the commercially available precursor *N*-(triphenylphosphoranylidene)aniline was previously reported to prepare acyclic ^{11}C-ureas from [^{11}C]CO_2 in moderate radiochemical yields (RCYs).[19] Del Vecchio *et al*. deployed *o*-azidoanilines and azido alcohols with dimethylphenylphosphine to synthesize cyclic ureas and carbamates, including oxatomide, domperidone, and zolmitriptan in useful yields through a proposed intramolecular Staudinger aza-Wittig sequence (SAW, Scheme 1a) upon heating to 70 °C.[20,21] An intermolecular variant of this reaction produced a linear carbamate in low RCY at much higher temperature.

We aimed to develop conditions that are high yielding and selective for C–O, C–N, C–C, and C–S bond formation and would be amenable for one-pot [^{11}C]CO_2-fixation to prepare radiopharmaceuticals and novel tracer candidates. Through the synthesis of functionalized iminophosphorane precursors, this approach would obviate the need for highly acidic $POCl_3$, Mitsunobu reagents, explosive azide precursors, and toxic phosphines used in current methodologies, enhancing the substrate versatility and practicality of this method for good manufacturing practices (GMP) environments (Scheme 1b). Herein, we describe a versatile and efficient approach to carbonyl ligation using iminophosphorane-CO_2-fixation coupled with intermolecular nucleophilic addition. This method is effective for synthesizing acyclic products with stable isotopes under mild conditions and is suitable for automated synthesis and ^{11}C radiolabeling. We demonstrate a broad substrate scope, high functional group tolerance, and practical application for the synthesis and isolation of radiopharmaceuticals.



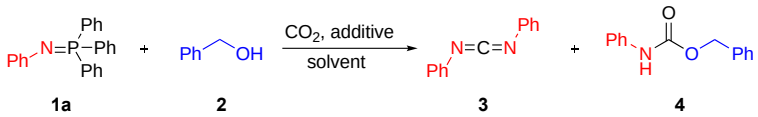
Scheme 1. Synthetic approaches to iminophosphorane [^{11}C]CO_2-fixation.

Results and Discussion

At the outset, we focused on developing a nucleophilic coupling strategy to iminophosphorane-CO_2 fixation conditions using stable isotopes, since no such straightforward high yielding

procedure for this coupling has been reported.[16] First, CO_2 was bubbled into a heated toluene solution containing *N*-(triphenylphosphoranylidene)aniline (**1a**) until complete consumption of the iminophosphorane, followed by the addition of benzyl alcohol (**2**).

Table 1. Optimization of reaction conditions



1a **2** **3** **4**

Entry	Solvent	[**2**] (mM)	**3** yield (%)	**4** yield (%)
1[a,b]	toluene	100	77	6
2[a,b]	toluene	150	77	6
3[a,c]	toluene	100	42	36
4[a,c]	toluene	250	0	84
5[d]	toluene	250	0	70
6[d]	1,4-dioxane	250	0	72
7[d]	DMF	250	0	75
8[d]	ACN	250	0	78
9[d,e]	ACN	250	0	84
10[d,f]	ACN	250	0	70

[a]Yields obtained by UPLC/MS. Reactions performed in toluene at 110 °C. [b]Nucleophile added after iminophosphorane consumption. [c]Nucleophile added at t = 0. [d]Conditions: **2** (0.625 mmol), solvent (2.5 mL), 85 °C; then **1** (100 mM, 2.5 mL) added over 1 h. Reaction time: 2 hr. Isolated yields. [e]DBU (2.6 equiv). [f]BEMP (2.6 equiv.)

Low yield of the desired product **4** (6%) was observed using stepwise addition (Table 1, entry 1). The observed major product was the symmetrical *N*,*N*′-diphenylcarbodiimide (CDI, **3**), likely formed by a second aza-Wittig coupling reaction to the isocyanate intermediate.[18] The ratio of **4**:**3** increased to 0.9:1 when the nucleophile was present from the beginning of the reaction (entry 3). Increasing the concentration of **2** led to exclusive formation of **4** in 84% yield (entry 4). This suggests that short-lived free isocyanates are formed in the presence of iminophosphoranes, subject to two competing reaction pathways: CDI formation and carbamate formation. Thus, at high

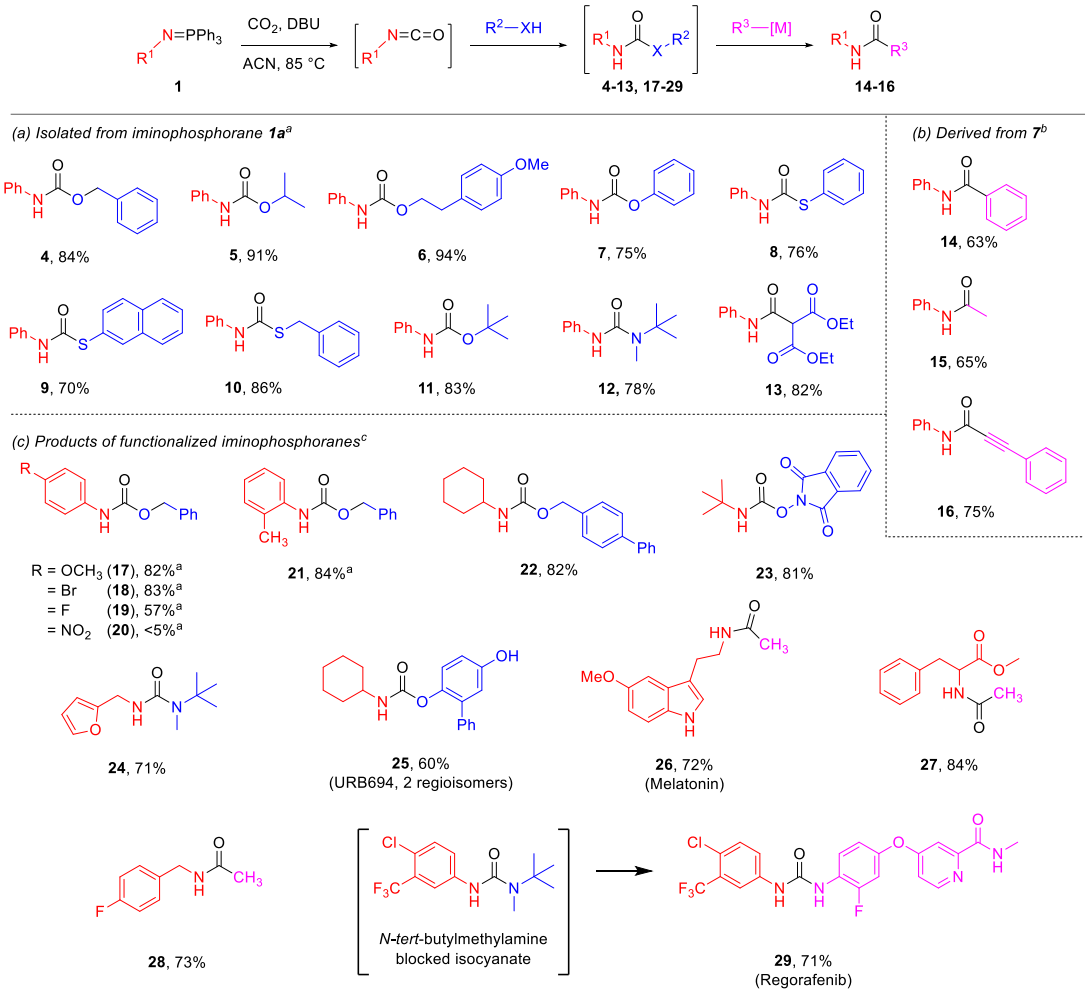
concentrations of an intercepting nucleophile, it is possible to selectively divert the reaction towards intermolecular ligation. Carbamate **4** could be prepared and isolated in good yields from hydrocarbon, ethereal, and polar solvents using similar conditions (entries 5–8). With our primary focus on establishing easily translatable conditions to ^{11}C radiochemistry, we were delighted to find that two common CO_2 trapping bases, amidine DBU and phosphazene BEMP (2.6 equiv.), significantly increased the rate of formation of **4**, concomitant with moderate impacts in yield (entries 9–10, table S1). These effects are likely due to the increased availability of soluble CO_2 in the form of activated complexes.[22,23]

We assessed the compatibility of the iminophosphorane-CO_2-fixation method with a diverse scope of nucleophiles (Scheme 2a). Under our developed conditions, carbamates derived from benzyl, isopropyl, and 4-methoxyphenethyl alcohol were isolated in 84–94% yields (**4-6**). In contrast, phenyl carbamates and thiocarbamates (**7-9**) required higher nucleophile concentrations to achieve yields in excess of 70%, likely due to their propensity for elimination. Benzyl mercaptan also proved to be a compatible nucleophile, forming the corresponding thiocarbamate **10** in excellent yield (86%). Sterically hindered nucleophiles such as *tert*-butanol yielded product **11** (83%) in high yield, and *N*-methyl-*N*-*tert*-butylamine also provided the urea **12** in 78% yield. We were gratified to find that amides such as **13** (82%) could be accessed directly by carbon-carbon bond formation using diethyl malonate. Despite this success, some nucleophiles were found to be incompatible with the interrupted aza-Wittig conditions, including Grignard reagents, and phenylacetylene. However, a number of our synthesized products (**7-9**, **11-12**) stand in as blocked isocyanates, and facilitate indirect nucleophilic substitution (Scheme 2b).[24] *In situ* formed *O*-phenylcarbamate **7** could be successfully transformed to amides **14**–**16**, all in moderate to good

yields based on iminophosphorane **1a**. Overall, both direct and indirect nucleophilic substitutions are robust, and further open the door to selective C-C bond formation using iminophosphoranes.

We next investigated the scope of functionalized aryl iminophosphoranes synthesized by the Kirsanov reaction and isolated by our modified general procedure (Scheme 2c, see ESI for details).[18] First, CBz-protected products (**17-21**) were isolated to determine sensitivity to electronic and steric features of iminophosphoranes under the optimized conditions. Electron-rich arenes, aryl bromides, and *ortho*-substitution (**17-18**, **21**) were all well-tolerated in comparison with electron-deficient iminophosphoranes (**19**–**20**). Alkyl iminophophosphoranes afforded products such as carbamate **22** (82%) and blocked isocyanates **23**–**24** in good yields. The utility of this method for biopharmaceuticals was assessed by targeting the fatty acid amide hydrolase inhibitor URB694 (**25**), melatonin (**26**), and the oral multi-kinase inhibitor regorafenib (**29**). Hydroquinone carbamate **25** was isolated as a mixture of regioisomers in 60% yield.[11] Indirect substitution using phenol-blocked isocyanates yielded melatonin **26** (72%), phenylalanine derivative **27** (84%), and electron-deficient amide **28** (73%). Finally, the urea regorafenib **29** was synthesized first by direct nucleophilic coupling, though indirect substitution using an *N*-*tert*-butylmethylamine blocked isocyanate intermediate better facilitated purification of **29** in 71% overall yield.[25]

Scheme 2: Interrupted aza-Wittig for Extended Functionality: Reaction Scope

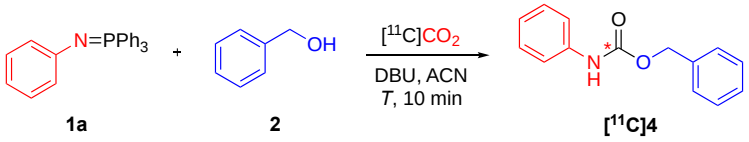


[a]Conditions: **1** (0.25 mmol), R^2-XH (2.5 equiv.), DBU (2.6 equiv.), ACN (2.5 mL), reflux; isolated yields. [b] PhOH (10 equiv.), R^3-MgX (20 equiv.) or R^3-SH (2.5 equiv.) or PhCCH (12 equiv.), THF. [c] R^2-XH (10 equiv.), LHMDS (0.99 equiv.), THF. See ESI for detailed procedures.

Satisfied with the iminophosphorane-CO_2 nucleophilic coupling methodology using stable isotopes, we were determined to apply this method to carbon-11 radiochemistry. Since [^{11}C]CO_2 is the limiting reagent in these processes (typically <1 μmol), reconsideration of reaction

conditions to produce [^{11}C]**4** was required (Table 2). First, we focused on the influence of the concentration of **1a** on product yield using high concentrations of DBU and benzyl alcohol in ACN (entry 1). We noted a low 13% RCY with these initial conditions, mainly due to a large excess of unreacted [^{11}C]CO_2. Increasing the concentration of **1a** (entries 2–3) led to maximum 32% RCY and reducing the concentration of DBU to 100 mM enhanced the selectivity toward [^{11}C]**4** (entry 4–5). Increasing the reaction temperature in DMF to 100 ºC resulted in 65% RCY (entries 6–7). Finally, increasing the concentration of nucleophile **2** further improved the selectivity of [^{11}C]**4**, leading to a 91% RCY (entries 7–9). Trapping efficiencies of [^{11}C]CO_2 during the optimization of [^{11}C]**4** were all greater than 90%.

Table 2. Radiochemistry Optimization



1a **2** **[^{11}C]4**

Entry	*T* (°C)	[**1a**] (mM)	[**2**] (mM)	[DBU] (mM)	RCY[a] (%)
1	65	7	200	200	13
2	65	70	200	200	32
3	65	100	200	200	29
4	65	70	200	150	39
5	65	70	200	100	56
6[b]	65	70	200	100	62
7[b]	100	70	200	100	65
8[b]	100	70	600	100	78
9[b]	100	70	1200	100	91

[a]Radiochemical yield calculated from relative integration of HPLC-UV chromatogram. [b]Reaction performed in DMF.

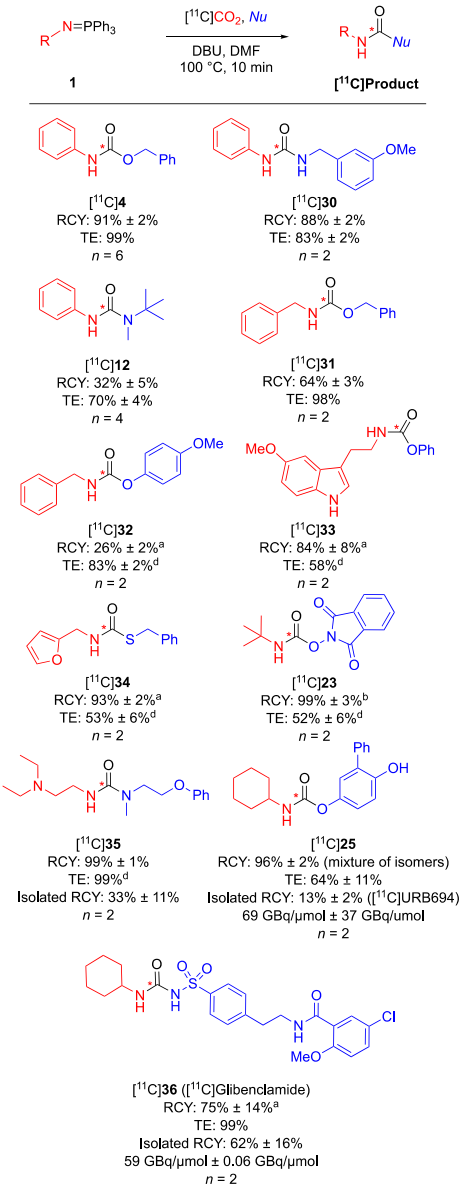
Structurally diverse iminophosphoranes were also used to successfully radiolabel compounds using this procedure (Scheme 3). Aniline derived products using iminophosphorane **1a** include labeled urea [^{11}C]**30** in 88% RCY, and blocked isocyanate [^{11}C]**12** in 32% RCY. Using

benzyl iminophosphorane, *O*-benzyl carbamate [^{11}C]**31** was formed in 64% yield. By substituting DABCO for DBU, *O*-aryl carbamate [^{11}C]**32** (26%), 5-methoxytryptamine carbamate [^{11}C]**33** (84%), and thiocarbamate [^{11}C]**34** (93%) could be radiolabeled, with trapping efficiencies ranging from 53–83%. We suspect that mildly basic conditions and higher nucleophile concentrations improve the yields of **32-34** due to their sensitivity towards low temperature elimination.[26] From *tert*-butyl iminophosphorane, *N*-hydroxysuccinimide-derived [^{11}C]**23** (99%) was also efficiently radiolabeled.

To further demonstrate the practicality of this technique [^{11}C]**35**, an experimental antiarrhythmic compound, also containing the ß-glucocerebrosidase activating moiety *N*-methyl-*N*-(2-phenoxyethyl)amine, was isolated using a fully automated method (see ESI).[27,28] [^{11}C]**35** was labeled with 99% RCY starting from 15.7 GBq of [^{11}C]CO_2, and obtained in an isolated yield of 33% ± 10.6% (2.7 ± 0.4 GBq) within 22 min from [^{11}C]CO_2 delivery. The fatty acid amide hydrolase inhibitor [^{11}C]URB694 ([^{11}C]**25**, [^{11}C]CURB) is used in clinical research studies to investigate psychiatric illnesses and alcohol use disorder, and was prepared from cyclohexyliminophosphorane in 96% ± 2% RCY (2:3 regioselectivity).[29,30] From 25.9 GBq of [^{11}C]CO_2, 1.9 GBq ± 0.7 GBq of [^{11}C]CURB was obtained as the major isomer in 99% radiochemical purity, with an isolated decay corrected yield of 13% ± 2%, and a molar activity of 69 GBq·µmol^{-1} ± 37 GBq·µmol^{-1} within 17 min from [^{11}C]CO_2 delivery. Lastly, the clinically approved sulfonylurea glibenclamide, currently used in the treatment of diabetes mellitus type 2, and shown to reduce tissue damage in preclinical models for CNS injuries, was synthesized with 75% ± 14% RCY.[31] [^{11}C]Glibenclamide ([^{11}C]**36**) is a substrate for organic anion-transporting polypeptide (OATP) transporter and can be used to study the integrity of the blood-brain barrier by non-invasive PET imaging.[32,33] This radiopharmaceutical, which is currently synthesized in

two-steps using [^{11}C]CH_3OTf, was efficiently labeled using an iminophosphorane precursor directly from [^{11}C]CO_2.[34] Following purification 7.4 ± 1.9 GBq of [^{11}C]glibenclamide was obtained with an isolated decay corrected yield of 62 ± 16% from 25.9 GBq of [^{11}C]CO_2, and a molar activity of 59 ± 0.06 GBq·μmol^{-1} within 21 minutes from the beginning of synthesis.

Scheme 3**: Carbon-11 Substrate Scope**



[a] DBU replaced with DABCO. [b] DBU replaced with LHMDS. [c] KO^{t}Bu. [d] [^{11}C]CO_2 trapped at -60 ºC. See ESI for detailed procedures. * indicates position of ^{11}C.

Conclusion

In conclusion, we have developed a methodology to synthesize several stable and radiolabeled functional groups using the interrupted aza-Wittig approach. The advantages of this method include direct [^{11}C]CO_2-fixation using stable iminophosphorane precursors prepared from commercially available amines, diverse functional group selectivity, and applicability to relevant PET imaging agents. Radiopharmaceuticals are synthesized under mild reaction conditions with rapid synthesis times and using automated procedures to represent a novel strategy for labeling biologically relevant molecules. We anticipate this method contributing to the accessibility of in-demand radiopharmaceuticals such as [^{11}C]CURB and [^{11}C]glibenclamide, among others.

Supporting Information

Characterization data; experimental procedures; preparation of precursors; NMR spectra for compounds

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Notes

The authors declare no competing financial interest.

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