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Continuous Flow Synthesis of Non-Symmetrical Ureas from CO₂

Alexandre Labiche,^[a] Maylis Norlöff,^[a] Sophie Feuillastre,^[a] Frederic Taran,^[a] Davide Audisio*^[a]

[a] A. Labiche, M. Norlöff, Dr. S. Feuillastre, Dr. F. Taran, Dr. D. Audisio*
Université Paris Saclay, CEA
Département Médicaments et Technologies pour la Santé, SCBM,
91191 Gif-sur-Yvette (France)
E-mail: davide.audisio@cea.fr

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Abstract: We report on a continuous flow synthetic process of non-symmetrical ureas, based on the implementation of a Staudinger/aza-Wittig reaction sequence. This flow technology allows obtaining the key urea functional group directly from the fundamental C1 building block CO₂. A library of 24 derivatives, including alkyl/alkyl, alkyl/aryl and aryl/aryl ureas could be synthesised. In addition, the methods was also suitable for the synthesis of *S*-thiocarbamates. The potential for large-scale reaction implementation and a first application to continuous flow ¹³C-isotope labeling are shown.

Introduction

Carbon dioxide (CO₂) is an advantageous C1 building block with a low toxicity profile, widely used by the chemical industry to produce important building blocks such as urea, methanol, salicylic acid, formaldehyde, formic acid, cyclic carbonates and dimethyl carbonate for instance.¹ While the electrophilicity of CO₂ was recently shown to be comparable to benzaldehyde,² the lack of thermodynamic driving force remains a challenge for its synthetic functionalization. Nonetheless, interest in transformations involving CO₂ witnessed a remarkable progress and a large variety of novel reactions has been reported.^{3,4,5,6} Furthermore, carbon isotopomers of CO₂ are of crucial importance in the field of ¹¹C, ¹³C and ¹⁴C labeling, as they represent the main primary sources of these isotopes.^{7,8}

Urea derivatives are a remarkable class of organic molecules and a functional group present in multiple compounds of interest and particularly in medicinal chemistry.^{9,10} According to a recent study by Ertl *et al.*, urea represents the 14th most frequent functional group occurring in bioactive molecules described in medicinal chemistry literature.¹¹ The presence of the carbonyl hydrogen bond acceptor and up to two hydrogen bond donors (for disubstituted derivatives) allows modulating the properties of this pharmacophore and improving the drug potency or receptor target interactions. As such, this moiety figures in a variety of biologically active compounds, such as anticancer,¹² antibacterial agents¹³ and HIV protease inhibitors for example.¹⁴

Not surprisingly, plethora of synthetic methods exists to access this functional group.¹⁵ In our longstanding research program aiming to use CO₂ as valuable building block in organic synthesis, we aimed to devise a sustainable technology that would allow accessing to substituted and non-symmetrical urea derivatives,

under safe conditions, avoiding use of poisonous reagents (as phosgene and carbon monoxide), with potential for simple scale-up implementation. In this context, the use of continuous flow chemistry was appealing, due to the practical and safer set-up for gas-liquid reactions on a laboratory scale. Indeed, continuous flow systems permit to improve the interfacial mixing, which plays a critical role in phase transfer.¹⁶ In addition, flow chemistry procedures can easily be automatized, thus helping reducing time consumption and offering high reproducibility and easier scalability. Besides, the use of a backpressure regulator (BPR) allows the control of the gas stoichiometry and the use of high-pressure environment, thus increasing the solubility of gases into liquid phases.¹⁶

In this report, we describe a continuous flow synthesis of non-symmetrical ureas utilizing CO₂ as key building block.¹⁷ This process, based on a Staudinger/aza-Wittig sequence, enabled to obtain a library of 24 derivatives containing both aliphatic and (hetero)aromatic substituents. The potential for scalability of the procedure was showcased and, by carefully controlling the gas-flow, a rare and interesting application of flow chemistry to the isotopic labeling of the carbonyl moiety with carbon-13 was performed.

Synthesis of urea derivatives in continuous flow chemistry have been reported and they rely essentially on the reactivity of isocyanates, either using commercially available sources or prepared in flow conditions. In 2008, Ley and co-workers proposed two strategies to synthesised isocyanates *in-situ* via a Curtius rearrangement at 120 °C, over 20 to 50 min. In the first strategy, an acyl chloride crossed a column packed with an azide ion-exchanged monolith to form acyl azide intermediates. After rearrangement, the formed isocyanate reacted with an amine to form the desired urea derivatives in 10 min at 100 °C, using a batch microwave system (Figure 1A).¹⁸ In a second procedure, they synthesised the acyl azide intermediate from a carboxylic acid and diphenylphosphoryl azide (DPPA). After the Curtius rearrangement, amines attack the isocyanate to form the desired ureas (Figure 1B).¹⁹ In 2017, Bana *et al.* investigated a microfluidic procedure starting from Boc-protected amines and 2-chloropyridine to form, in presence of a dehydrating agent (Tf₂O), the desired isocyanate in a first micro-reactor. Next, excess of amine (up to 9 equiv.) was added into the isocyanate stream to react in a second micro-reactor forming urea derivatives (Figure 1C).²⁰ On the other hand, an alternative strategy was reported by Rutjes to access libraries of urea derivatives based on the

piperidin-4-one scaffold, using a flow process with commercial isocyanates.²¹ In a similar fashion, the group of Ulven prepared a series of piperazine urea compounds directly from the available isocyanates.²²

While no example of continuous flow synthesis of ureas directly from CO₂ has been reported, traditional batch methodologies using this C1 building block are well-established.²³ Most of the published methods often require harsh reaction conditions (high temperatures and/or CO₂ pressures) and are essentially limited to symmetrical ureas and display poor functional group tolerability.^{24, 25} For example, the group of Stephan described in 2019 the synthesis of symmetric urea derivatives from CO₂ and silylamines.²⁶ While very effective, this procedure is applicable only to symmetrical ureas, is performed at 120-150 °C and needed excess of CO₂ (2 to 5 atm). To access unsymmetrical, structurally more complex ureas, the use of iminophosphoranes has attracted attention due to their ability to undergo an aza-Wittig reaction in presence of CO₂.^{27, 28} In 2013, the group of Cravotto²⁹ published a microwave-assisted Staudinger/aza-Wittig (SAW)

reaction to prepare urea derivatives from azides, using supported diphenylphosphine under 14 bars of CO₂ pressure at 50 °C. Recently, our group and others have shown that this strategy is suitable to the synthesis of carbon isotope labeled ureas. Under optimized conditions, the SAW reaction proceeds under exceptionally mild conditions (room temperature, 5 minutes) and using CO₂ as limiting reagent.³⁰ In 2022, this strategy was used by the group of Morandi to develop a selective molecular CO₂ sensing technology,³¹ and Ohata and co-workers have recently shown its potential for protein and DNA bioconjugation.³²

While the SAW reaction has shown to be a powerful tool to access urea derivatives from CO₂, applications to isotope labeling are usually performed on limited scale. The use of a continuous flow system might offer a novel solution to synthesise larger amounts of product while taking advantage of the versatility of this transformation.³³

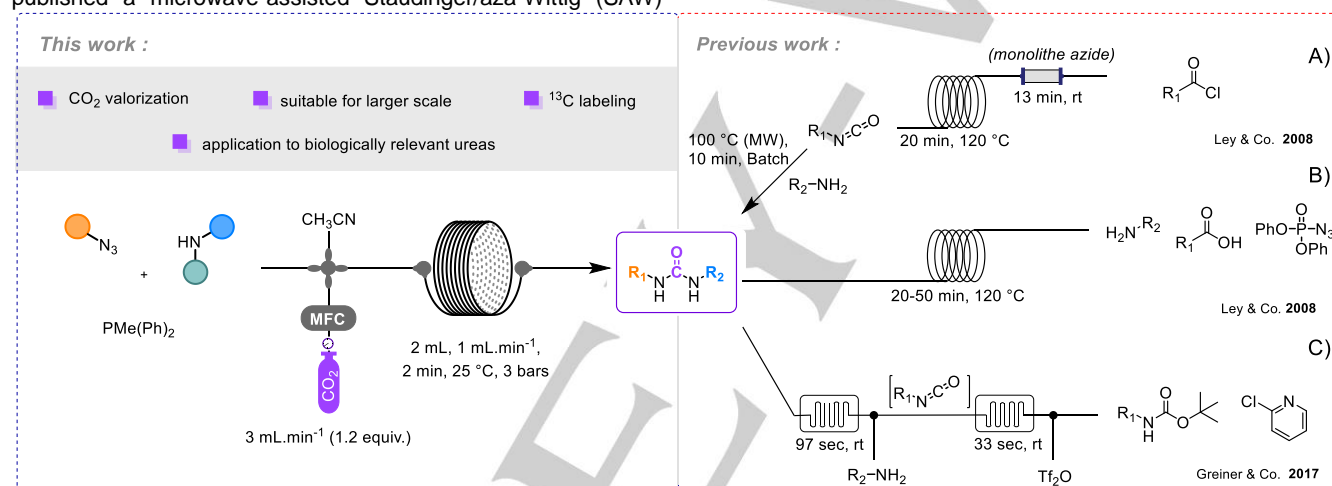


Figure 1. Continuous flow synthesis of non-symmetrical ureas via isocyanate formation. DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; CH₃CN, Acetonitrile; MW, Microwave.

Results and Discussion

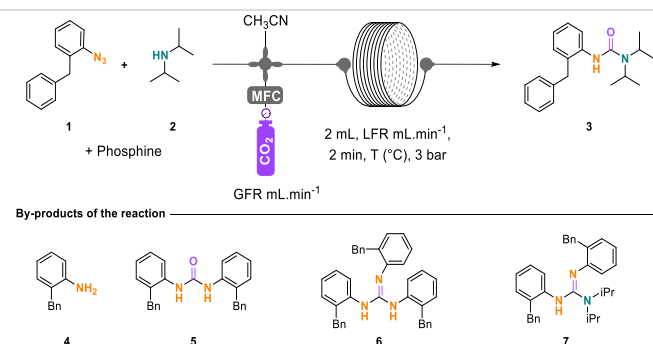
We started our investigations using conditions inspired by previous *batch* results obtained on the model reactants 1-azido-2-benzylbenzene (**1**) and diisopropylamine (**2**).^{30b} In presence of dimethylphenylphosphine (DMPP) in dry ACN (0.1 M), using CO₂ gas and liquid flow rates of 3 and 1 mL min⁻¹, respectively (corresponding to 1.2 equivalents of CO₂)³⁴ and a residence time of 2 minutes at 25 °C, with a BPR stabilized at 3 bars, 70% yield of desired urea **3** was obtained (entry 1, Table 1). While satisfying, a number of secondary by-products were formed during the process, including aniline **4** coming from the Staudinger reduction, the corresponding symmetrical urea **5**, as well as guanidines **6** and **7**, formed from the reaction of the transient iminophosphorane with the isocyanate generated *in situ*. In order to increase the yield and limit the formation of such by-products, we attempted to optimize further the reaction. Representative entries of the optimization are shown in Table 1 and in the supporting information.

Beside the pressure, the increase of the temperature is known to affect the solubility of CO₂ in organic solvents.³⁵ When the temperature of the reaction was raised up to 100 °C, we observed a deleterious effect on the yield, and we noticed an increased formation of aniline **4** (entries 1-3, Table 1).

Increasing of the gas flow rate (GFR) did not improve the yield (entries 5 and 6, Table 1), as CO₂ was already present in slight excess (1.2 equivalent with 3 mL.min⁻¹). When GFR is decreased to 1 mL.min⁻¹ (*i.e.* to 0.4 equivalents of CO₂, entry 4, Table 1), the yield dropped to 42%. Next, we observed that when the liquid flow rate (LFR) was increased, the yield decreased noticeably (entries 7 and 8, Table 1). This relies to lack of CO₂ equivalents in the reaction,³⁴ as confirmed by the presence of unreacted iminophosphorane and reduced amine **4** in the crude mixture (entry 9, Table 1). Subsequently, we analysed the effect of pressure on the system. When P < 3 bars, a slug flow stream was observed at the out port, whereas when P > 3 bars, the flow seemed more annular (no visible bubbles) (Supp. Info, Table S1, entry 6). Decreasing the concentration of the sample (Supp. Info, Table S1, entries 2-3) and varying the pressure at the BPR (Supp.

Info, Table S1, entries 6, 8, 9) did not influence the yield of the reaction. Finally, a series of monodentate phosphines were screened (entries 10-12, Table 1). While a poor yield was observed in presence of triphenylphosphine (TPP), as the corresponding iminophosphorane requires a higher temperature to react efficiently with carbon dioxide,^{30a,36} we were pleased to see that methyldiphenylphosphine (MDPP) provided an improved yield of 80%. Here, MDPP (methyldiphenylphosphine) provided the best balance between the reactivity in the Staudinger reduction, the stability of the corresponding iminophosphorane and its nucleophilicity.³⁷

Table 1. Optimization for the synthesis of urea in continuous flow^[a]



Entry	T (°C)	GFR (mL/min)	LFR (mL/min)	Phosphine	Yield (%) ^[b]
1	25	3	1	DMPP	70
2	50	3	1	DMPP	60
3	100	3	1	DMPP	25
4	25	1	1	DMPP	42
5	25	5	1	DMPP	64
6	25	7	1	DMPP	74
7	25	3	0.1	DMPP	49
8	25	3	2	DMPP	67
9	25	3	4	DMPP	21
10	25	3	1	TPP	10
11	25	3	1	MDPP	80
12	25	3	1	DPPP	50

[a] Conditions: 0.1 mmol of 1 azido-2-benzylbenzene **1**, 0.1 mmol of diisopropylamine **2**, 0.1 mmol of phosphine, in 1 mL of CH₃CN (0.1 M), the pressure inside the device was 3 bars, the volume of the reactor is 2 mL and the residence time was 2 min [b] NMR yield using dibromomethane as internal standard. GFR = Gas Flow Rate. LFR = Liquid Flow Rate. DMPP = dimethylphenylphosphine, TPP = triphenylphosphine, MDPP = methyldiphenylphosphine, DPPP = diphenylpropylphosphine

Having established a convenient and reliable procedure for the synthesis of urea **3**, we aimed to establish the scalability of the process. As shown in Figure 2A, the highest yields were obtained by scaling up the process from 1.0 mmol to 5.0 mmol until a plateau of 80% yield, which is in agreement with NMR yields measured. A productivity of 6 mmol · h⁻¹ could be reached showing the potential of this method for scaling-up synthesis.

With this optimized set of conditions, we next explored the scope of the reaction and its limitations (Figure 2B, 2C and 2D). Using the 1-azido-2-benzylbenzene **1** as model azide, primary and benzylic amines (**3**, **8**, **9**), as well as secondary aliphatic amines, including cyclic amines, such as azetidine and morpholine, proved suitable and allowed to isolate the corresponding ureas **8-12** in 62 to 73% yield. The use of hydrazines was tolerated and the desired semicarbazides **13** and **14** were obtained in 41% and

53% yields, respectively. On the other hand, highly sterically hindered cyclic amines such as 2,2,6,6-tetramethylpiperidine (**31**) were unproductive.

Next, various substitutions on the azide moiety were explored, both with aromatic and aliphatic derivatives. In agreement with our previous findings, the presence of electron-donating groups (EDG) on the aromatic azide favoured the formation of the product (**16**, 80% yield). In contrast, with 1-azido-4-bromobenzene the yield dropped significantly under standard conditions (**15**). Moreover, alkylazides allowed obtaining the corresponding ureas **17-21** in 27% to 75% yield. Notably, 1-azidoadamantane in presence of *s*-butylamine allowed isolating product **19** in 59% yield. The presence of heterocyclic moieties such as coumarin and pyridine were well tolerated, as ureas **22** and **23** were isolated in 81% and 67% yield. Subsequently, we looked to anilines as nucleophilic partners. While indoline proved suitable under standard conditions and urea **24** was obtained in 56% yield, aryl/aryl ureas (**25** and **26**) gave only traces amounts of the desired products, at room temperature. According to the study reported by Babin *et al.*,^{30b} excess of the nucleophile (2 equiv.) at 80 °C and the use of *N*-methylimidazole were used in order to enhance the reactivity of anilines. Under such conditions, the flow reaction allowed isolating **25** and **26** in 34% and 54% yield, respectively. Besides amines, the process was suitable to the intramolecular reaction in presence of *o*-azidophenol, and compound **30** was isolated in 51% yield.³⁶ On the other hand, alcohols and carboxylic acid containing amines were unsuccessful (**34**, **35** and **36**). In contrast, we were pleased to see that thiols allowed isolation of the corresponding *S*-thiocarbamates **27** and **28** in satisfying yields. By means of the current technology, biologically relevant compounds such as herbicide Diuron **29**, Chlorzoxazone **30** (an FDA approved drug displaying muscle relaxant properties)³⁸ and compound **31**, a recently reported inhibitor of *Acinetobacter baumannii*,³⁹ could be obtained in one single step from CO₂. RTICBM-189 (**32**), a Cannabinoid Type-1 receptor (CB1) negative allosteric modulator (NAMs), was shown by Zhang and co-workers to attenuate reinstatement of cocaine-seeking behaviour.⁴⁰ Using the current flow system, RTICBM-189 was obtained in 70% yield on a 0.3 mmol scale. Pleasingly, when the reaction was scaled at on 4.6 and 9.0 mmol the desired compound was obtained in 65% and 74% yield corresponding to 0.92 and 2.06 grams of final product. Notably, the compound could be purified by simple filtration, as compound **30** precipitated directly in the crude reaction mixture.

A straightforward access to ¹³C-labeled compounds is of paramount importance in medical science. Stable labeled ¹³C-molecules are used as internal standards to conduct targeted metabolomics studies, where the qualification of various metabolites is pivotal.⁴¹ Moreover, Absorption, Distribution, Metabolism and Excretion (ADME) studies, as well as mass balance studies, can be performed using stable ¹³C-labeled products.⁴²

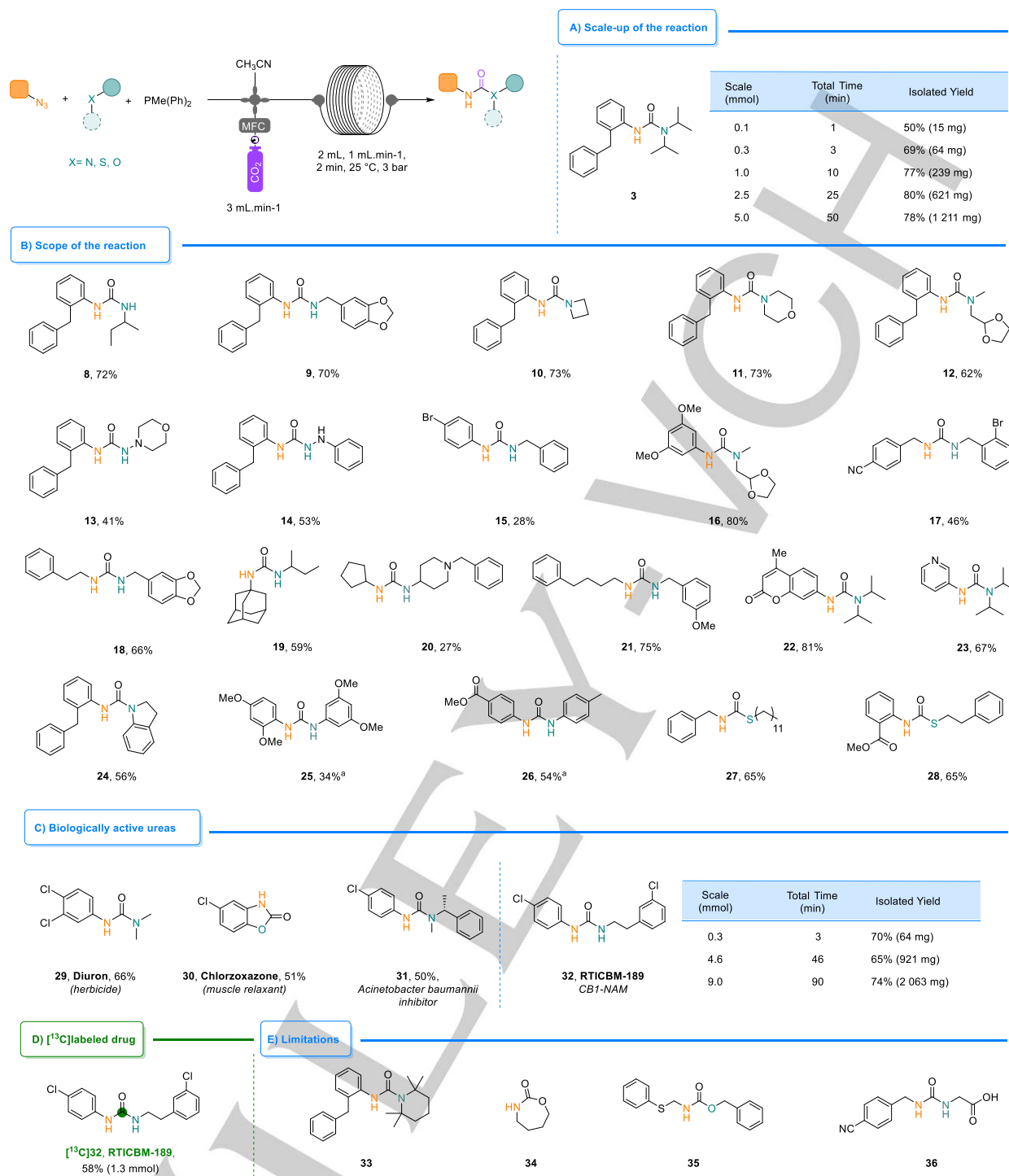


Figure 2. Synthesis of various urea derivatives, molecules of interest and scale-up. Conditions: azide (1.0 equiv., 0.3 mmol), amine or thiol or alcohol derivatives (1 equiv., 0.3 mmol), methyl diphenyl phosphine (1 equiv., 0.3 mmol), dry CH₃CN (0.1 M, 3 mL). Reactions occur in a 2 mL standard coil reactor from Vapourtec®, 25 °C, gas (CO₂) flow rate at 3 mL min⁻¹, liquid flow rate at 1 mL min⁻¹, 3 bars. a) Azide (1.0 equiv., 0.3 mmol), amine (2 equiv. 0.6 mmol), 1-methylimidazole (2 equiv., 0.6 mmol), methyl diphenyl phosphine (1 equiv., 0.3 mmol), dry CH₃CN (0.1 M, 3 mL).

When using naturally abundant [¹²C]CO₂, usually excess of the reagent is utilized, as costs of the gas are disregarded. In stark contrast, for the isotopically labeled counterpart the higher price of the starting material⁴³ requires a careful reconsideration of the gas stoichiometry. Flow chemistry is an ideal tool as the ¹³C-labeled gas bottle can be easily connected through a pressure regulator to a mass flow controller and therefore to the flow system. Under the optimized conditions, it was therefore possible

to use the gas with a stoichiometric amount by setting a specific gas flow rate. We were pleased to isolate [¹³C]RTICBM-189 in 58% yield on a 1.3 mmol scale using 1.2 equivalents of [¹³C]CO₂

Conclusion

In conclusion, a continuous flow synthesis of non-symmetrical ureas was developed, based on the implementation of the well-

known Staudinger/aza-Wittig reaction. Compared to the state of the art, this technology allows obtaining the key urea functional group directly from the fundamental C1 building block CO₂. After optimization, this procedure allowed to synthesise a library of 24 derivatives, including alkyl/alkyl, alkyl/aryl and aryl/aryl ureas. In addition, the method was also suitable to the synthesis of S-thiocarbamates. Application to the synthesis of biologically active ureas was successfully implemented and RTICBM-189 (**32**) a Cannabinoid Type-1 receptor (CB1) negative allosteric modulator (NAMs) was obtained on a 9 mmol scale (2 grams) and isolated by simple precipitation. As the optimized protocol was carefully chosen to limit the equivalents of CO₂ (1.2 equivalent of gas), a first application of continuous flow ¹³C-labeling was also shown.

Experimental Section

Into a vial, the azide (1.0 equiv.) is dissolved in dry CH₃CN (0.1 M). Then, the amine (1.0 equiv.) and the methylphenylphosphine (1.0 equiv.) were added to the solution. The mixture was then transferred inside Vapourtec injection loops. The liquid flow rate (dry CH₃CN) and the gas flow rate (CO₂) was set up at 1 mL.min⁻¹ and 3 mL.min⁻¹ respectively. A Mass Flow Controller (MFC) was used to obtain a regular gas flow rate. The liquid and the gas phases were mixed using a Y-mixer and went through a 2mL Vapourtec® coil at room temperature. A Back Pressure Regulator (BPR) set up at a fixed pressure of 3 bars ended the set-up (Figure S1, Supp.Info). The crude product was purified by flash Chromatography or precipitation depending on the urea.

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Keywords: Continuous Flow Chemistry • Carbon Dioxide • Staudinger-Aza-Wittig • Non-Symmetrical Ureas • Carbon-13

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