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High-Efficiency Aminocarbonylation by Introducing CO to a Pressurized Continuous Flow Reactor

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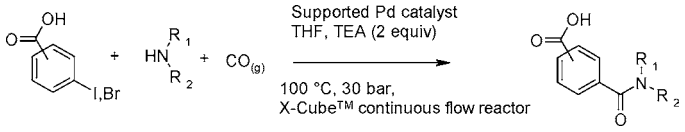
ABSTRACT



Halogenated aryl carboxylic acids were efficiently converted to the corresponding dicarboxylic acid monoamides by a one-step Pd-catalyzed aminocarbonylation in a micro/meso fluidic continuous flow reactor (X-Cube) operated at high pressure and high temperature with CO gas introduction. Reaction parameters (solvent, base, catalyst, pressure, temperature) were rapidly optimized in the reactions, which required less than 2 min. The method gave improved results over comparable batch techniques and is also suited to automated parallel syntheses of compound libraries.

The syntheses of selectively derivatized dicarboxylic acids hold considerable interest because of their common occurrence as biologically active compounds in medicinal chemistry, for example, 1,1-cyclohexanediacetic acid monoamide (gabapentine) is an important neurological agent[1] and terephthalic acid monoamides have antiallergic effects,[2,3] and some dicarboxylic acids are inhibitors of dicarboxylate monoamide aminohydrolases.[4] In addition, they can often be found in materials derived from natural sources.[5,6] The conventional synthesis of aryl dicarboxylic acid monoamides is usually achieved via three steps,[7,8] with selective deprotection of diesters[9,10] followed by amidation and a second deprotection.[11] While the carbonylation of aryl halides, a versatile reaction, is an important synthetic route for the preparation of aromatic carboxylic acid derivatives, like carboxylic amides,[12−27] the direct aminocarbonylation of

(1) International Patent, Publication No. CA2371210: Process for the preparation of pharmaceutical grade Gabapentin.

(2) U.S. Patent 4642375: Process for preparing derivatives of the monoamide of terephthalic acid.

(3) U.S. Patent 4221814: Terephthalic acid monoamide derivatives, process for preparing the same, and an anti-allergic agent prepared from the same.

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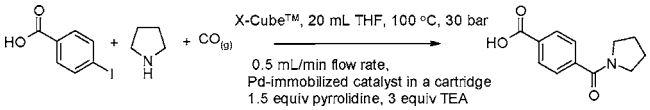
haloaryl acids for synthesis of a dicarboxylic acid monoamide has only been mentioned in a single paper.[28]

We considered the one-step selective syntheses of dicarboxylic acid monoamides an important chemical problem so we tried to solve it by direct CO gas introduction using our continuous flow system. We selected the aminocarbonylation of 4-iodobenzoic acid with pyrrolidine and carbon monoxide as a model reaction to demonstrate the optimization of the reaction conditions (Scheme 1) because this was

Scheme 1. Model Reaction[a]



[a] X-Cube is a trademark of ThalesNano Inc., Hungary. It is a high-pressure continuous-flow reactor capable of reaching temperatures and pressures between room temperature and 200 °C and up to 150 bar, respectively, and performing reactions with or without gas introduction from an external source. The system works by flowing substrates through a low-volume stainless steel reaction line and reacting them continuously on preloaded catalyst/reagent cartridges.

the single example quoted in the literature.[28] In this study, we applied a continuous flow reactor.[29]

This general-purpose flow chemistry instrument (X-Cube) works by pressing the solution of substrates through a low-volume stainless steel tube and reacting them continuously on preloaded catalyst cartridges under high pressure, high temperature, by optional continuous gas introduction.[30−32] In our model reaction, we introduced carbon monoxide from an external cylinder.

Intelligent solvent selection is essential in flow chemistry as precipitates can easily block the narrow tubes used. A range of solvents often used for cross-coupling reactions was tested, including acetonitrile, acetone, 1,4-dioxane, and tetrahydrofuran (THF). THF was found to offer the best solubility of both starting materials and products. Next, the most effective base needed to be determined. Model reactions were run using different organic bases such as *N*-methylpyrrolidine (NMPY), triethylamine (TEA), 1,4-diazabyciclo-[2.2.0]octane (DABCO), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), and *N*-ethyldiisopropylamine (EDIPA). The results listed in Table 1 indicated TEA was the best base to be used in this reaction. Several catalysts were also screened to find the one most

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Table 1. Results of Comparing Different Bases

base	conversion[a] (%)
NMPY	68
TEA	83
DABCO	47
DBU	0
DMAP	44
EDIPA	33

[a] Conversion to 4-(pyrrolidine-1-carbonyl)benzoic acid.

suitable for this flow based synthesis. Hence, a selection of commercially available immobilized palladium catalysts was used to fill the proprietary cartridges (CatCarts, a trade name by ThalesNano, Inc., Hungary). The best results were obtained with polymer-supported tetrakis(triphenylphosphine)palladium, which resulted in high conversion with no detectable byproduct under the test conditions (Table 2).

Table 2. Results of Comparing Different Immobilized Catalysts

catalyst	conversion[a] (%)
$Pd(TPP)_4$[b]	83
FibreCat 1001[c,g]	25
FibreCat 1007[d,g]	9
PdEnCat TPP 30[e,h]	20
PdEnCat 30[f,h]	2

[a] Conversion to 4-(pyrrolidine-1-carbonyl)benzoic acid. [b] FibreCat 1001: $Pd(OAc)_2$/TPP on polymer fiber. [c] FibreCat 1007: $Pd(OAc)_2$/tricyclohexylphosphine on polymer fiber. [e] PdEnCat TPP 30: microencapsulated $Pd(TPP)_4$. [f] Pd EnCat 30: microencapsulated $Pd(OAc)_2$. [g] FibreCat is a registered trademark of Johnson Matthey, Inc., UK. [h] EnCat is a trademark of Reaxa Ltd., UK.

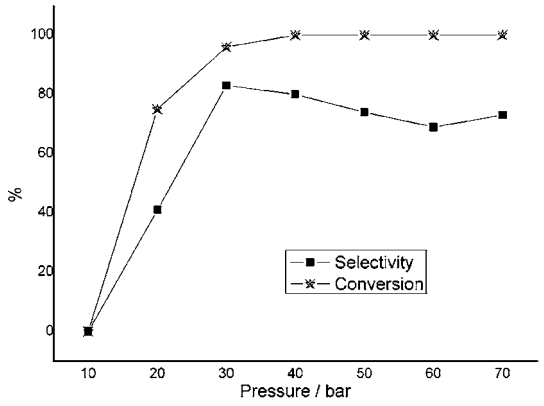


Figure 1. Effect of pressure. Reaction conditions: 0.01 M of 4-iodobenzoic acid in 20 mL of THF, 1.5 equiv of pyrrolidine, 2.0 equiv of base, $Pd(TPP)_4$ catalyst (CatCart), 100 °C, 0.5 mL/min flow rate.

The effect of pressure up to 70 bar and of temperature between 25 and 100 °C was also studied. Testing at higher temperatures was limited due to the decomposition of the applied polymer supported catalysts that can occur above

100 °C. Due to the high system pressure, all reactions could be run in the liquid phase even above the boiling point of tetrahydrofuran. Figures 1 and 2 summarize the effect of

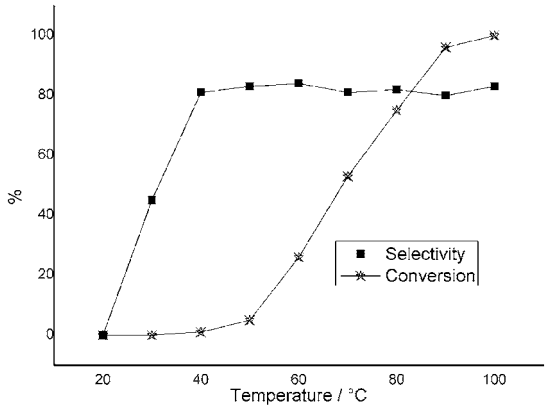


Figure 2. Effect of temperature. Reaction conditions: 0.01 M of 4-iodobenzoic acid in 20 mL of THF, 1.5 equiv of pyrrolidine, 2.0 equiv of base, $Pd(TPP)_4$ catalyst (CatCart), 30 bar, 0.5 mL/min flow rate.

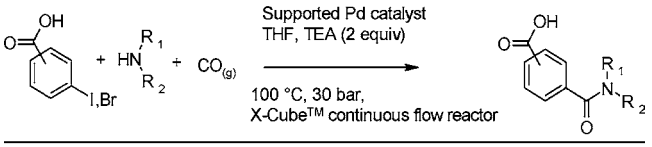
temperature and pressure. The conversion (as defined by the percentage transformation of the starting material to all new compounds) was significantly increased at higher pressures and temperatures and reached 100% above 40 bar and 90 °C respectively. The selectivity toward the desired product was optimal at 30 bar CO pressure. The decline of selectivity over 30 bar suggested that the reaction kinetics may change at higher pressure, and there was a detectable byproduct (terephthalic acid).

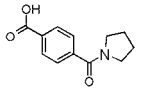
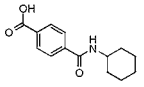
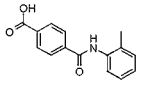
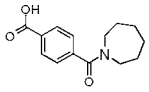
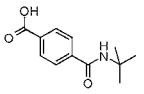
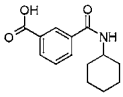
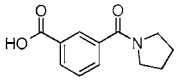
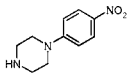
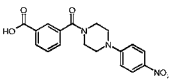
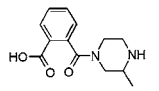
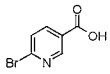
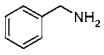
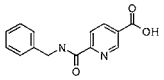
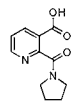
Table 3. Comparison of Flow and Batch Reactions

	conversion[a] (%)	selectivity[b] (%)
autoclave[f,i]	22[c]	36[c]
	60[d]	20[d]
balloon[g,j]	35[c]	54[c]
	69[d]	75[d]
flow[h]	96[e]	87[e]

[a] Conversion to all new compounds. [b] Percent of desired product (4-(pyrrolidine-1-carbonyl)benzoic acid). [c] After a sampling at 30 min. [d] Reaction time was 60 min. [e] Reaction time (i.e., residence time) was 1.5 min. [f] Temperature 100 °C, pressure 30 bar. [g] Temperature 68 °C (reflux), pressure ca. 1 bar. [h] Temperature 100 °C, pressure 30 bar, flow rate: 0.5 mL/min. [i] 4-Iodobenzoic acid (1 mmol, 0.248 g), pyrrolidine (1.5 mmol, 124 μL), and triethylamine (2 mmol, 278 μL) were dissolved in 50 mL of tetrahydrofuran. The solution was placed into an ultrasonic degasser for 10 min. Then the solution was moved to a glovebox (under a nitrogen atmosphere). The catalyst (0.4 g tetrakis(triphenylphosphine)palladium) was added into the reaction mixture. The autoclave (with 250 mL volume) was closed and filled to 30 bar with carbon monoxide and stirred at 100 °C for 1 h. The reaction mixture was then cooled to room temperature. The autoclave was opened in a fume hood and the catalyst was filtered from suspension. [j] The solution prepared as above was purged with carbon monoxide in a balloon for 15 min. The catalyst was added and stirred under a CO balloon at reflux (68 °C) for 1 h.

Table 4. Results of Various Monoamide Syntheses



Aryl-halogenide	Amine	Product	Isolated yield[a] (%)
			81
			73
			69
			58
			63
			50
			61
			61
			25
			69
			32
			56
			30

[a] After purification by preparative HPLC.

The typical protocol for aminocarbonylation when optimizing the model reaction in X-Cube was the following: 4-iodobenzoic acid (1 mmol, 0.248 g), pyrrolidine (1.5 mmol, 124 μL), and triethylamine (2 mmol, 278 μL) were dissolved

in 50 mL of tetrahydrofuran. The solution was passed through X-Cube with 0.5 mL/min flow rate at 100 °C and 30 bar. Carbon monoxide gas from a cylinder was introduced to the X-Cube, which mixed the CO gas with the solution in its gas−liquid mixer unit. The gas−liquid mixture then was pressed through the prefilled, preheated cartridge (CatCart, containing 0.4 g of catalyst) where the reaction took place. The reaction time (as calculated from the residence time) was less than 2 min. The solvent was removed under reduced pressure, resulting in a product of 75% purity and 96% conversion. Preparative HPLC chromatography (with Waters 2545-ZQ 4000 system) purification afforded the product, 4-(pyrrolidine-1-carbonyl)benzoic acid (0.177 g) in 81% yield in over 98% purity.

To compare our approach with traditional batch carbonylation methods,[33] we carried out the same reaction (Scheme 1) in a pressurized autoclave and in a conventional flask using a CO-filled balloon. Table 3 shows the results of the comparative tests where we found a remarkable difference in favor of the flow technique.

In summary, the flow chemistry provided higher selectivity and conversion rate than conventional batch methods within a shorter time. The efficiency of the synthesis in the flask was also limited by the boiling point of tetrahydrofuran (68 °C) as the reaction temperature.

As an important factor of safety, the total volume of the carbon monoxide present at a time of the system was 800 mL in the flow reaction with X-Cube vs 7500 mL in an autoclave and 1000 mL in a glass flask.

After optimizing the reaction conditions as described above, a derivatized dicarboxylic acids series was synthesized in the X-Cube reactor without further optimization, under the conditions optimized for the synthesis of 4-(pyrrolidine-1-carbonyl)benzoic acid.

The conversions and yields were acceptable (Table 4), taking into consideration the large structural diversity of the compounds studied (some halobenzoic and halonicotinic acids with a collection of primary, secondary, and aromatic amines). The amidocarbonylation by continuous flow works well with iodobenzoic acid isomers and relatively reactive amines (for example, pyrrolidine, benzylamine, and cyclohexylamine), while bromonicotinic acids and iodobenzoic acids with amines of low reactivity (*tert*-butylamine and 4-nitrophenylpiperazine) resulted in lower conversion and yield. With three exceptions (e.g., in the formation of 3-[4-(4-nitrophenyl)piperazine-1-carbonyl]benzoic acid, which resulted in contaminants such as regioisomers), all the other transformations showed high purity toward the desired products.

In conclusion, we have shown that flow chemistry using X-Cube gave remarkable results for carbonylative coupling reactions of halobenzoic acids with amines. Reaction parameters (solvent, base, catalyst, pressure, temperature) were rapidly optimized in the reactions, which required less than 2 min. The short time of optimization allowed to a large number of optimizing reactions and facilitated generalization of the experiences. The method gave improved results over comparable batch techniques and is also suited to automated parallel syntheses of combinatorial libraries.[34]

Acknowledgment. We thank Dr. András Kotschy from Eötvös Loránd University and Tom Smith from the Thalesnano UK office for their valuable contributions to the preparation of this manuscript.

Supporting Information Available: Experimental details for the aminocarbonylation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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