



Double carbonylation of iodobenzene in a microfluidics-based high throughput flow reactor

János Balogh^a, Árpád Kuik^a, László Üрге^b, Ferenc Darvas^b, József Bakos^a, Rita Skoda-Földes^{a,*}

^a University of Pannonia, Institute of Chemistry, Department of Organic Chemistry, P.O.Box 158, H-8201 Veszprém, Hungary

^b ThalesNano Inc., Záhony u. 7., H-1031 Budapest, Hungary

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ABSTRACT

Double carbonylation of iodobenzene in the presence of amines were carried out effectively in a microfluidics-based flow reactor (X-Cube™) of high throughput capability using immobilized Pd(PPh₃)₄ catalyst. By the proper tuning of the reaction conditions α -ketoamides could be synthesized with 70–96% selectivities depending on the choice of the nucleophile. The highest yields of double carbonylation products were obtained at relatively low temperature (80 °C) and using DBU as the base with primary amines as the reaction partners. Imine formation was observed only at higher temperatures.

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1. Introduction

Since its discovery by Ozawa [1] the palladium-catalyzed double carbonylation of aryl halides to give α -keto acids, esters and amides has been extensively studied [2]. The products are versatile intermediates in organic synthesis of α -hydroxy acids and α -amino acids. However, there are some problems associated with double carbonylation, such as the need of relatively complicated experimental manipulation under high pressure conditions and the difficulty in catalyst recovery.

Although both Uozumi [3] and ourselves [4] have shown that double carbonylation can be carried out occasionally with satisfactory selectivity even at atmospheric pressure, in most cases high pressure conditions are required to promote double carbonylation with reasonable selectivity.

Besides, most studies on carbonylation reactions are focused on using homogeneous catalysts that are difficult to separate from non-volatile products and cannot be reused. Although there are a few examples for alkoxy- or aminocarbonylation reactions carried out in the presence of heterogenized catalysts [5], reports concerning the application of the same method for double carbonylation are scarce [6].

The use of a microfluidics-based flow reactor (X-Cube™ [7]) offers an elegant solution for both of the problems mentioned

above. It ensures a safe and easy manipulation of carbon monoxide of high pressure as well as the use of immobilized catalysts placed in CatCart™ cartridges. Moreover, it enables the synthesis of chemical libraries of a great number of products in a short time and optimization of reaction conditions in minutes.

Here we report our results on the aminocarbonylation and double carbonylation reactions of iodobenzene in the presence of various amines carried out in the flow reactor X-Cube™ using immobilized Pd(PPh₃)₄ catalyst. A detailed investigation of the effects of the changes in the reaction conditions (temperature, flow rate, nucleophile and base) has been carried out.

2. Experimental

All reagents were good quality commercial products and were used as received without further purification. Toluene was distilled over sodium benzophenone ketyl and stored under argon before use.

2.1. Catalytic experiments in the flow reactor

The reactions were carried out in the microfluidics-based flow reactor in continuous flow mode. Commercially available immobilized Pd(PPh₃)₄ placed into 70 mm × 8 mm CatCart™ cartridges (0.4 g, loading capacity 0.7 mmol/g) were used as catalyst. The catalyst bed was washed continuously with the toluene solutions of aryl halide (0.05 M), amine (0.05 M or 0.1 M), and base (0.1 M) with flow rates between 0.2 and 0.5 ml/min. Carbon monoxide was mixed

* Corresponding author. Tel.: +36 88 624719; fax: +36 88 624469.
E-mail address: skodane@almos.uni-pannon.hu (R. Skoda-Földes).

with the liquid flow before entering the CatCart™ where the pressure was adjusted to 40 bar and the temperature was regulated in the range of 70–100 °C.

Reaction mixtures were analyzed by gas chromatography (Hewlett Packard 5890) and GC–MS (Hewlett Packard 5971A GC–MSD, HP-1 column). Conversions and selectivities of the reactions were determined by GC using ferrocene as internal standard.

The products **3–5** were identified on the basis of their MS spectra.

3a: MS(*m/z*/rel.int.): 191 (M^+)/18; 190/49; 176/10; 105/100; 77/63.

3b: MS(*m/z*/rel.int.): 203 (M^+)/36; 122/94; 105/100; 77/72.

3c: MS(*m/z*/rel.int.): 161 (M^+)/9; 146/8; 105/100; 77/64.

3d: MS(*m/z*/rel.int.): 177 (M^+)/9; 162/5; 148/6; 135/23; 134/21; 105/100; 77/42.

4a: MS(*m/z*/rel.int.): 219 (M^+)/6; 114/22; 105/100; 77/44.

4b: MS(*m/z*/rel.int.): 231 (M^+)/23; 105/100; 77/41.

4c: MS(*m/z*/rel.int.): 189 (M^+)/6; 105/100; 77/58.

4d: MS(*m/z*/rel.int.): 205 (M^+)/17; 105/100; 77/36.

5b: MS(*m/z*/rel.int.): 312 (M^+)/25; 186/27; 104/100; 77/5.

5c: MS(*m/z*/rel.int.): 228 (M^+)/8; 144/100; 104/72; 77/15.

5d: MS(*m/z*/rel.int.): 260 (M^+)/6; 217/21; 160/36; 104/100; 77/10.

2.2. Catalytic experiments in an autoclave (batch reactions)

In a typical experiment iodobenzene (0.2 mmol), Pd(PPh₃)₄ (0.01 mmol), the amine (0.4 mmol), DBU (0.4 mmol) and toluene (4 ml) were transferred under an inert atmosphere into a stainless steel autoclave. It was charged with carbon monoxide (40 bar) and heated with stirring in an oil bath at 60 °C for 4 h.

Reaction mixtures were analyzed by gas chromatography (Hewlett Packard 5890). Conversions and selectivities of the reactions were determined by GC using ferrocene as internal standard.

2.3. Synthesis of **6**

Iodobenzene (0.4 mmol), Pd(PPh₃)₄ (0.02 mmol), DBU (1.0 mmol) and toluene (4 ml) were transferred under an inert atmosphere into a stainless steel autoclave. It was charged with carbon monoxide (40 bar) and heated with stirring in an oil bath at 100 °C for 8 h. The product was purified by column chromatography (silica, CHCl₃/MeOH = 40/1). Yield = 20%.

6: ¹H NMR(CDCl₃) δ: 7.93 (brs, 1H, NH); 7.85–7.89 (m, 2H, Ph); 7.36–7.38 (m, 3H, Ph); 3.44–3.46 (m, 2H, C(O)NCH₂); 3.28–3.38 (m, 4H, CH₂NCH₂); 2.50–2.53 (m, 2H, C(O)CH₂); 1.60–1.74 (m, 8H, 4CH₂). MS(*m/z*/rel.int.): 274 (M^+)/29; 246/6; 217/8; 177/10; 162/18; 140/82; 105/100; 77/76.

3. Results

Carbonylation of aryl halides (e.g. **1** or **2** Scheme 1) in the presence of secondary amines usually leads to a mixture of mono- (**3**) and dicarbonylated products (**4**). Chemoselectivity of the reaction depends greatly on the reaction conditions: temperature, base and the nature of the nucleophile. The use of primary amines as the nucleophilic reaction partners is usually avoided. The latter reaction is less selective at elevated temperatures due to a condensation reaction of the α-ketoamide product with the excess of the amine leading to imines (**5**) as side products.

Recently, we have observed a marked effect of the temperature on the selectivity of aminocarbonylation of iodobenzene [4] and iodoferrrocene [8]. At low temperatures (60 °C and below) the main products are the α-ketoamides in most cases, while at 100 °C the formation of the amides is favoured.

There are somewhat contradictory results in the literature concerning the effect of the base. Uozumi found DABCO the most effective base promoting selective α-ketoamide formation during atmospheric carbonylation of iodobenzene with *n*-butylamine at room temperature, while in the presence of DBU the amide was formed as the main product [3]. On the contrary, Inoue reported on the beneficial effect of DBU on double carbonylation of iodobenzene with diethylamine as the nucleophile. In this reaction the use of DABCO resulted in the formation of equal amounts of the two products [9].

Considering these results, we focussed on the clarification of the effects of the temperature and the base on the selectivity of the carbonylation reaction using the X-Cube™ flow reactor. As carbonylation was expected to be more problematic with primary amines as nucleophiles (see above), in addition to the secondary amine morpholine, the selectivity of the reaction was investigated using cyclohexylamine, allylamine and *n*-butylamine as the reaction partners.

As it was expected, the modification of the temperature resulted in a change not only in the conversion but also in the selectivity of the reaction. Appreciable conversions were achieved above 70 °C (Table 1, entries 1 and 2). As it was observed earlier for batch reactions [4,8], the ratio of α-ketoamides decreased with increasing temperature in all cases. Primary amines were more apt to undergo double carbonylation than morpholine.

The use of a higher amine/substrate ratio led to higher conversion and improved selectivity for the α-ketoamide, although the extent of the change was different with morpholine and cyclohexylamine. In the first case, the ratio of α-ketoamide increased considerably (entries 2–7), while only a slight improvement was observed for the reaction of cyclohexylamine (entries 15–17 and 20–22).

Increased flow rates (0.5 ml/min instead of 0.2 ml/min) led to a decrease in the conversion of the substrate and in the selectivity for the α-ketoamide (entries 18 and 19).

Using triethylamine as the base, monocarbonylation is favoured at all temperatures in the reactions of morpholine (entries 1–7) and also above 80 °C in those of cyclohexylamine (entries 16, 17, 21, 22). DBU was proved to induce the best selectivity for α-ketoamides using both morpholine (entry 11) and cyclohexylamine (entry 26) as the nucleophiles. At 80 °C **4a** and **4b** were obtained with 70% and 87% selectivities, respectively. DABCO was less effective: **3a** and **4a** were obtained in nearly equal amounts at all temperatures (entries 8–10) and although double carbonylation was favoured at 80 °C in the reaction of cyclohexylamine (entry 23), selectivity fell behind that obtained with DBU. Markedly improved conversions were obtained using either DABCO or DBU compared to those achieved with Et₃N and total conversion of iodobenzene was observed in the presence of these two bases at 90 °C and above.

Similar conclusions can be drawn from the results of carbonylation with allylamine or *n*-butylamine nucleophiles in the presence of either Et₃N or DBU as the base. The use of DBU led to excellent selectivities for the α-ketoamides at 80 °C in both cases (entries 33 and 40).

However, DBU cannot be considered as an innocent base under carbonylation conditions. As it has been observed before during aminocarbonylation of iodoferrrocene [10], DBU can be acylated by the palladium(II)-acyl complex formed in the reaction of the palladium(0) precursor, iodobenzene and CO producing **6** after the opening of the bridge of the bicyclic moiety (Scheme 2). **6** was isolated in 20% yield in a batch reaction of **1**, DBU and CO in the presence of Pd(PPh₃)₄ at 100 °C and was proved to be present in some of the reaction mixtures containing DBU (entries 12, 13, 27, 28, 34, 35, 41 and 42) by GC–MS measurements.

Fortunately, **6** was produced only in 2–4% in the reactions carried out in the flow reactor at 90–100 °C. As a comparison, batch reactions led to this side product in 8–19% yield.

Table 1
Carbonylation of iodobenzene (**1**) bromobenzene (**2**) in the flow reactor^a.

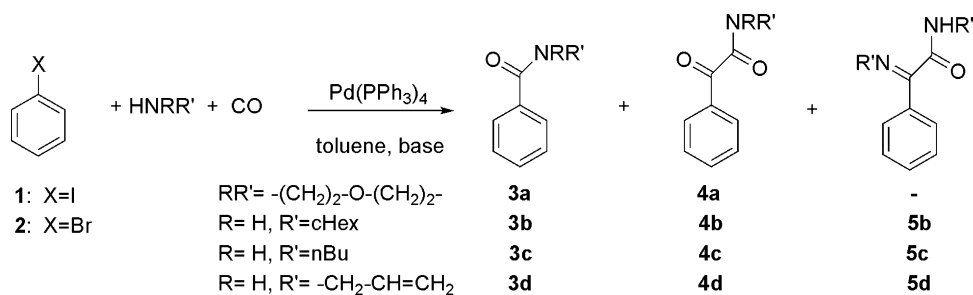
| Entry | Substrate | Amine | Amine/substrate | Base | Temp. (°C) | Conv. (%) ^b | Selectivity (%) ^b | | | | | | |
|-----------------|-----------|------------------|----------------------|-------------------|-------------------|------------------------|------------------------------|-----|-----|----|----|----|---|
| | | | | | | | 3 | 4 | 5 | 6 | | | |
| 1 | 1 | Morpholine | 1 | Et ₃ N | 70 | 6 | 71 | 29 | | | | | |
| 2 | | | | | 80 | 31 | 79 | 21 | | | | | |
| 3 | | | | | 90 | 49 | 98 | 2 | | | | | |
| 4 | | | | | 100 | 64 | 100 | 0 | | | | | |
| 5 | | | | | 2 | Et ₃ N | 80 | 35 | 58 | 42 | | | |
| 6 | | | | | | | 90 | 53 | 63 | 37 | | | |
| 7 | | | | | | | 100 | 74 | 76 | 24 | | | |
| 8 | | 2 | DABCO | 80 | | | 80 | 46 | 56 | | | | |
| 9 | | | | 90 | 100 | 59 | 41 | | | | | | |
| 10 | | | | 100 | 100 | 63 | 37 | | | | | | |
| 11 | | 2 | DBU | 80 | 61 | 30 | 70 | | – | | | | |
| 12 | | | | 90 | 100 | 33 | 65 | | 2 | | | | |
| 13 | | | | 100 | 100 | 38 | 59 | | 3 | | | | |
| 14 ^c | | | | 60 | 97 | 16 | 69 | | 15 | | | | |
| 15 | 1 | Cyclohexyl-amine | 1 | Et ₃ N | 80 | 22 | 42 | 58 | – | | | | |
| 16 | | | | | 90 | 40 | 80 | 20 | – | | | | |
| 17 | | | | | 100 | 79 | 91 | 9 | – | | | | |
| 18 ^d | | | | | 80 | 13 | 75 | 25 | – | | | | |
| 19 ^d | | | | | 100 | 30 | 100 | 0 | – | | | | |
| 20 | | | | | 2 | Et ₃ N | 80 | 61 | 38 | 62 | – | – | |
| 21 | | | | | | | 90 | 72 | 72 | 28 | – | – | |
| 22 | | 100 | 89 | 85 | | | 15 | – | – | | | | |
| 23 | | 2 | DABCO | 80 | | | 96 | 24 | 76 | – | – | | |
| 24 | | | | 90 | 100 | 57 | 43 | – | – | | | | |
| 25 | | | | 100 | 100 | 62 | 38 | – | – | | | | |
| 26 | | 2 | DBU | 80 | 92 | 13 | 87 | – | – | | | | |
| 27 | | | | 90 | 100 | 20 | 75 | 3 | 2 | | | | |
| 28 | | | | 100 | 100 | 35 | 57 | 4 | 4 | | | | |
| 29 ^c | 60 | | | 83 | 18 | 52 | 11 | 19 | | | | | |
| 30 | 1 | Allylamine | 2 | Et ₃ N | 80 | 25 | 25 | 75 | – | | | | |
| 31 | | | | | 90 | 46 | 88 | 12 | – | | | | |
| 32 | | | | | 100 | 76 | 99 | 1 | – | – | | | |
| 33 | | | | | 2 | DBU | 80 | 64 | 9 | 91 | – | – | |
| 34 | | | | | | | 90 | 98 | 39 | 58 | – | 3 | |
| 35 | | | | | | | 100 | 100 | 55 | 38 | 3 | 4 | |
| 36 ^c | | | | | | | 60 | 87 | 11 | 71 | 4 | 14 | |
| 37 | | 1 | <i>n</i> -Butylamine | 2 | Et ₃ N | 80 | 40 | 39 | 61 | – | | | |
| 38 | | | | | | 90 | 88 | 68 | 23 | 9 | | | |
| 39 | | | | | | 100 | 98 | 76 | 13 | 11 | | | |
| 40 | | | | | | 2 | DBU | 80 | 76 | 4 | 96 | – | – |
| 41 | | | | | | | | 90 | 100 | 38 | 54 | 6 | 2 |
| 42 | | | | | | | | 100 | 100 | 53 | 33 | 12 | 2 |
| 43 ^c | | | | | | | | 60 | 93 | 23 | 61 | 8 | 8 |
| 44 | 2 | Morpholine | 1 | Et ₃ N | 80 | <3 | | | | | | | |
| 45 | | | | | 90 | 9 | 86 | 14 | | | | | |
| 46 | | | | | 100 | 11 | 88 | 12 | | | | | |
| 47 | 2 | Cyclohexyl-amine | 2 | DABCO | 80 | 43 | 48 | 52 | – | | | | |

^a Reaction conditions: 0.05 M iodobenzene in toluene, flow rate: 0.2 ml/min, substrate/base=1/2, 40 bar CO, catalyst: Pd(PPh₃)₄.

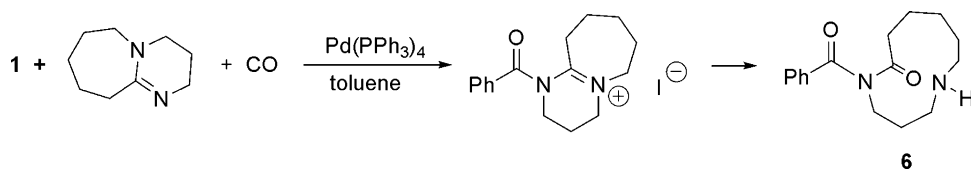
^b Determined by GC.

^c In an autoclave after 4 h.

^d Flow rate: 0.5 ml/min.



Scheme 1. Aminocarbonylation of aryl halides using secondary and primary amines as nucleophiles.



Scheme 2. Formation of **6** via carbonylation of iodobenzene (**1**) in the presence of DBU.

The formation of imines in the presence of primary amine nucleophiles was observed only at 90–100 °C in continuous flow carbonylations, while batch reactions led to these products in higher amounts even at 60 °C. The only exception is the reaction of *n*-butylamine where **5d** was produced with 11–12% and 8% selectivities in the reactions carried out in the microflow reactor at 100 °C and in the autoclave at 60 °C, respectively (entries 39, 42 and 43).

As a comparison, carbonylation of bromobenzene (**2**) was carried out, too, under certain reaction conditions (entries 44–47). As it was expected, bromobenzene was found to be less reactive than iodobenzene (**1**). Besides, selectivity of the reaction was found to be poorer in each case (compare entries 2–4 and 44–46; 23 and 47).

4. Conclusions

Double carbonylation of iodobenzene **1** in the presence of various amines was carried out with high selectivity in a microfluidics-based flow reactor (X-Cube™). The reactor could be used effectively for the optimization of aminocarbonylation of iodobenzene.

Excellent conversion of the substrate was observed in the temperature range 80–100 °C using either DABCO or DBU as the base. α -Ketoamides were produced with high selectivity at 80 °C, using an excess of the nucleophile in the presence of DBU. No side reactions leading to **6** or imines **5b–5d** were observed under these conditions. At the same time, high temperature, triethylamine as a base and the use of an equal amount of substrate and nucleophile

are the best reaction conditions to obtain the amides with good selectivity.

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