Tetrahedron 72 (2016) 7509–7516

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Substituent effects in aminocarbonylation of *para*-substituted iodobenzenes

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ARTICLE INFO

Article history:
Received 17 April 2016
Received in revised form 19 September 2016
Accepted 4 October 2016
Available online 8 October 2016

Keywords:
Palladium
Iodoarene
Carbonylation
Hammett constant
Carbon monoxide
Carboxamide

ABSTRACT

Iodobenzene derivatives possessing various substituents (amino, hydroxy, *tert*-butyl, methyl, isopropyl, phenyl, fluoro, chloro, methoxycarbonyl, acetyl, trifluoromethyl, nitro) in the *para* position were aminocarbonylated using *tert*-butylamine and *n*-butylamine as *N*-nucleophiles. A palladium(0) catalyst formed in situ from palladium(II) acetate and triphenylphosphine was used. Carboxamide and ketocarboxamide type compounds were formed via single and double carbon monoxide insertion, respectively. While 4-substituents with negative Hammett constants (σ_p) decrease reactivity of the substrates, the iodoaromatics possessing electron-withdrawing group (characterized by positive Hammett constants (σ_p)) in the 4-position have shown high reactivity. Highly active catalysts were obtained in the presence of *xantphos* accompanied by the chemoselective formation of the corresponding carboxamides. The difference in reactivity of iodoarene and bromoarene functionalities enabled the synthesis of bromo-substituted compounds suitable for further functionalization.

1. Introduction

Since the early discovery of Heck et al.[1] the Pd-catalyzed carbonylation of haloarenes of various structures have been carried out in the presence of alcohols and amines as *O*- and *N*-nucleophiles, respectively. This reaction has become one of the most powerful tools for the synthesis of aromatic carbonyl compounds such as esters and carboxamides. A broad variety of nucleophiles have been successfully employed in this transformation to furnish a diversity of products in both laboratory and industrial settings.[2] The seminal work of Yamamoto et al.[3] revealed several important details of double carbonylation of haloaromatics in the presence of amines, i.e., the formation of 2-ketocarboxamides.

During the past decades, palladium-catalyzed carbonylation reactions including amino- and alkoxycarbonylation have gained several applications in synthetic chemistry. Both the synthesis of simple building blocks and the functionalization of biologically important skeletons were accomplished.[4]

It is worth noting that in spite of the aminocarbonylation of iodoarenes resulting in carboxamide/2-ketocarboxamide mixtures, the alkoxy- and aminocarbonylation of iodoalkenes (and that of their synthetic surrogates, enol-triflates) gave α,β-unsaturated esters and carboxamides, respectively, in highly chemoselective reactions inserting a single carbon monoxide only.[5] It has been shown recently that in the presence of bulky phosphite ligands, even double carbon monoxide insertion can be achieved with iodoalkenes as substrates in aminocarbonylation.[6]

As for the recent achievements in this field, carbon-monoxide-free aminocarbonylation of a great variety of *N*-substituted formamides with aryl iodides and aryl bromides using palladium acetate and *xantphos* has been described. It has been proved by dozens of examples that this functionalization is applicable for a wide range of formamides and aryl halides under carbon monoxide-free carbonylation conditions.[7] Similarly, a palladium-*xantphos* catalyst was used for the transformation of α-bromomethyl sulfoxides, carbon monoxide, and *N*-nucleophiles to the corresponding α-sulfinyl amides. It is worth noting that it can be considered as the first example of aminocarbonylation using nonbenzylic sp^3-hybridized carbon.[8] ^{13}C- and ^{2}H-labeled phenethylamine derivatives were synthesized via carbonylation. The double carbonyl insertion, that is, the incorporation of two ^{13}CO into phenethylamines was accomplished using a palladium-catalyzed double carbonylation of aryl iodides.[9] A novel *N*-nucleophile, NaN_3 has been used in azidocarbonylation of iodoarenes at 1 bar carbon monoxide. The Pd-*xantphos* catalyzed reaction readily occurs in an organic solvent–H_2O biphasic system under ambient conditions. It has been revealed by detailed mechanistic investigations, employing DFT (BP86-D3) calculations that oxidative addition of iodoaromatics to Pd(0) is the rate-determining step. It has been proved by

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http://dx.doi.org/10.1016/j.tet.2016.10.004
0040-4020/

calculations that the oxidative addition is different under CO in excess and under CO deficient conditions: the Ar–I bond is activated by the carbonyl phosphine-palladium complex or by the carbonyl-free (*xantphos*)Pd(0) species, respectively.[10]

In this work, the influence of the *para*-substituents of iodobenzene derivatives on the chemoselectivity of aminocarbonylation and the reactivity of the substrate will be described.

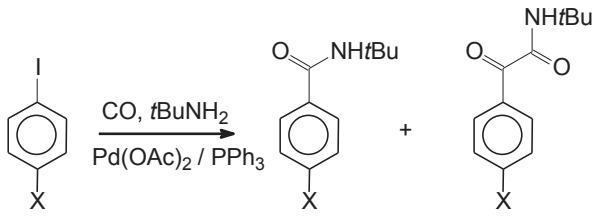
2. Results and discussion

2.1. Aminocarbonylation of 4-substituted iodobenzenes with *tert*-butylamine under atmospheric carbon monoxide pressure

Iodobenzene (**1a**) and its 4-substituted derivatives (**1b**–**1o**) were aminocarbonylated using *tert*-butylamine as *N*-nucleophile under an atmospheric pressure of carbon monoxide (Scheme 1).

More pronounced differences were obtained regarding the chemoselectivity of aminocarbonylation. In general, the aminocarbonylation of the substrates possessing electron releasing groups in the 4-position (e.g., **1d**, **1e**, **1f**) resulted in the preferred formation of ketoamides (**3**). It has to be added that the halide-substituted iodoarenes (**1h**, **1i**, **1j**) gave the highest ketocarboxamide/carboxamide ratio of ca. 4/1. However, those substrates with electron withdrawing groups (e.g., **1l**, **1m**, **1n**) provided reaction mixtures with slightly preferred formation of carboxamides (**2**).

Considering the range of the electronic properties of the substituents, 4-iodonitrobenzene would be expected also to provide a mixture of carboxamide and ketocarboxamide with preference for the carboxamide. However, the exclusive formation of carboxamide (**2o**) was observed in 4 h. It has to be added that in longer reaction times the partial reduction of the nitro functionality was also observed, i.e., some 4-amino derivative (**2b**, ca. 5%) was also detected.



1 **2** **3**

X = H (**a**), NH_2 (**b**), OH (**c**), *t*Bu (**d**), CH_3 (**e**), *i*Pr (**f**), Ph (**g**)
F (**h**), Cl (**i**), Br (**j**), $COOCH_3$ (**k**), $C(O)CH_3$ (**l**), CF_3 (**m**), CN (**n**), NO_2 (**o**)

Scheme 1. Aminocarbonylation of 4-substituted iodobenzenes with *tert*-butylamine.

Palladium(II) acetate served as a catalytic precursor for a highly active, coordinatively unsaturated palladium(0) catalyst.

According to a generally accepted mechanism,[2] palladium(0) catalysts are necessary to activate the starting iodoarene substrate. In these experiments, a highly active $Pd(OAc)_2$/2 PPh_3–type '*in situ*' catalyst was used which provided the low-ligated electron rich palladium(0) complex via reduction while one of the 2 equiv of phosphine ligands is oxidized to the corresponding phosphine oxide.[11]

As expected, the aminocarbonylation of iodoarenes (**1a**–**1o**) carried out *at atmospheric carbon monoxide pressure* resulted in the formation of a mixture of two types of carbonylated products: carboxamides (**2a**–**2o**) and 2-ketocarboxamides (**3a**–**3o**) were formed via mono- and double carbon monoxide insertion, respectively (Table 1). Although the main aim of this work was not the optimization of the synthesis of carbonylated products, it is worth noting that several 4-substituted carboxamides and ketocarboxamides (e.g., the 4-amino, 4-bromo, 4-hydroxy derivatives) isolated as analytically pure compounds can serve as synthetic building blocks. It has to be added that isolation and full characterization of the products were performed on the reaction mixtures obtained after practically full conversion (See Supplementary data).

As for the reactivity of the substrates, very similar conversions were obtained in those cases where no parallel reaction(s) of the substrate (vide infra) are expected. The conversions obtained in 4 h varied between 35 and 47%. As exceptions, highly reactive 4-iodoaniline (**1b**) and especially 4-iodophenol (**1c**) have to be mentioned. Substrate **1c** is almost completely converted to the corresponding amide and ketoamide products even in 2 h (for further conversion and selectivity data see also Supplementary Table S1).

2.2. Aminocarbonylation of 4-substituted iodobenzenes with *tert*-butylamine under 40 bar carbon monoxide pressure

The same substrates were aminocarbonylated using *high-pressure* (*40 bar*) *carbon monoxide* (Table 2). The formation of 2-

Table 1
Aminocarbonylation of 4-substituted iodobenzenes (**1a**–**1o**) in the presence of $Pd(OAc)_2$/2 PPh_3 'in situ' catalyst using *tert*-butylamine as *N*-nucleophile at atmospheric CO pressure[a]

Substrate	Hammett *para* constant	Conv.[b] [%]	TOF[c] [h^{-1}]	Ratio of the carbonylated products[b] [%]	
				Carboxamide (**2**)	Ketocarboxamide (**3**)
1a	0	35	3.5	22 (**2a**)	78 (**3a**)
1b	−0.66	27	2.7	60 (**2b**)	40 (**3b**)
1c	−0.37	>98	>9.8	80 (**2c**)	20 (**3c**)
1d	−0.20	35	3.5	27 (**2d**)	73 (**3d**)
1e	−0.17	46	4.6	30 (**2e**)	70 (**3e**)
1f	−0.15	39	3.9	26 (**2f**)	74 (**3f**)
1g	−0.01	43	4.3	36 (**2g**)	64 (**3g**)
1h	0.06	40	4.0	20 (**2h**)	80 (**3h**)
1i	0.23	42	4.2	25 (**2i**)	75 (**3i**)
1j	0.23	47	4.7	24 (**2j**)	76 (**3j**)
1k	0.45	39	3.9	51 (**2k**)	49 (**3k**)
1l	0.50	45	4.5	53 (**2l**)	47 (**3l**)
1m	0.54	46	4.6	51 (**2m**)	49 (**3m**)
1n	0.66	46	4.6	60 (**2n**)	40 (**3n**)
1o	0.78	49	4.9	100 (**2o**)	0 (**3o**)

[a] Reaction conditions (unless otherwise stated): 1 mmol substrate (**1a**–**1o**), 3 mmol of $tBuNH_2$, 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol of PPh_3, 0.5 mL of Et_3N, 10 mL of DMF, 50 °C, 1 bar CO, reaction time: 4 h.
[b] Determined by GC–MS.
[c] Moles of converted substrate/(moles of catalyst×time).