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Aminocarbonylation (hydrazinocarbonylation) of iodoalkenes and iodoarenes

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ABSTRACT

Iodoalkenes such as 1-iodocyclohexene, 4-*tert*-butyl-1-iodocyclohexene, α-iodostyrene and 17-iodoandrost-16-ene were aminocarbonylated in palladium-catalysed reaction using 1,1-disubstituted (cyclic) hydrazines (3-amino-3-azabicyclo[3.3.0]octane and (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)/(*R*)-1-amino-2-methoxymethyl-pyrrolidine (RAMP)) as *N*-nucleophiles. The corresponding hydrazides were formed in moderate to high yields. The hydrazinocarbonylation of iodobenzene using the above 1,1-disubstituted hydrazines resulted in a rather complex reaction mixture due to two major types of side-reactions: *i)* the deamination of the 3-amino-3-azabicyclo[3.3.0]octane, and *ii)* the double carbon monoxide insertion. In this way, in addition to the expected benzoylhydrazide derivative, phenylglyoxylhydrazide (double CO insertion product) and benzamide ('deamination' product) were also formed. By the appropriate modification of the reaction conditions, good selectivities towards the target compounds were achieved even in these cases. The formation of the products/side-products were rationalized on the basis of a simplified catalytic cycle.

1. Introduction

The widely used palladium-catalysed amino- and alkoxycarbonylation reactions of aryl halides are based on the seminal work of Heck et al. It was discovered that aryl halides, especially aryl bromides and iodides undergo carbonylation reaction in the presence of primary/secondary amines and alcohols used as *N*- and *O*-nucleophiles, respectively.[1] The synthetic importance of these reactions have been illustrated by the variation in structure of both the substrate and nucleophile.[2–6] These carbonylations are among the most important homogeneous catalytic reactions of synthetic importance and have found use in industrial applications.[7,8]

Soon after the discovery of aminocarbonylation of haloaromatics, their synthetic analogues, *i.e.*, iodo- and bromoalkenes as well as the corresponding enol-triflate surrogates have also been synthesised and transferred to the corresponding α,β-unsaturated carboxamides in palladium-catalysed aminocarbonylations.[5,6]

The synthesis of unsubstituted hydrazides is a straightforward methodology for aromatics, however quite difficult for α,β-unsaturated hydrazides which usually undergo undesired Michael-type cyclization.[9] Although the nucleophilic properties of alkyl- and aryl-hydrazine derivatives as well as the importance of their hydrazides are well known,[10] their synthesis via the corresponding ester needs special reaction conditions, for instance, the application of organoaluminium reagents.[11]

Although transition metal catalysed reactions could provide efficient solutions for the synthesis of carboxylic acid derivatives such as amides, esters, anhydrides, *etc.* from their building blocks, there are only a very few examples for the application of substituted hydrazines as *N*-nucleophiles in palladium-catalysed carbonylations. Steroidal hydrazides were prepared in hydrazinocarbonylation and used for further ring-closure reactions.[12–14] Diiodoaromatics were reacted with hydrazines under a carbon monoxide atmosphere leading to tetrahydrophthalazine derivatives.[15] Sulfonylhydrazides (aminosulfonamides) were synthesised in palladium-catalysed reactions using $(SO_2)_2$·DABCO adduct as sulfur dioxide source and the corresponding 1,1-disusbstituted hydrazines.[16]

As a part of our systematic investigations regarding structure–reactivity and structure–selectivity relationships in palladium-catalysed carbonylation reactions, the above 1,1-disubstituted hydrazines of practical interest[17,18] were used. It is worth noting that

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the iodoalkene-based aminocarbonylation reaction, described below provided a facile methodology even for the otherwise hardly available α,β-unsaturated hydrazides.

2. Results and discussion

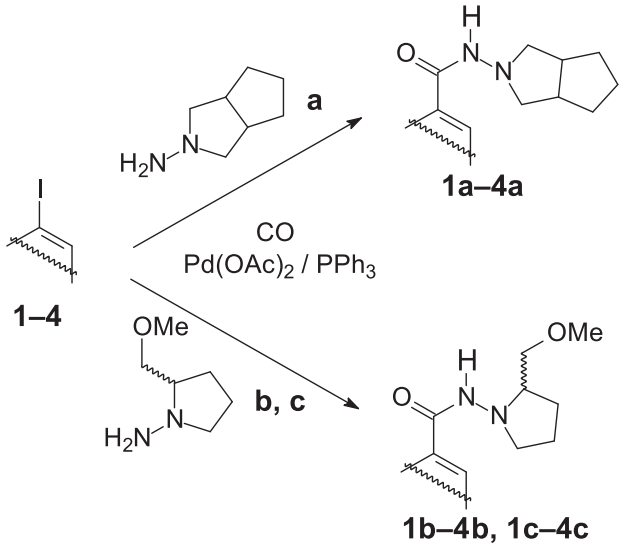
2.1. Aminocarbonylation of iodoalkenes in the presence of 3-amino-3-azabicyclo[3.3.0]octane and SAMP/RAMP as cyclic (1,1-substituted) hydrazines

1-Iodocyclohexene (**1**), 4-*tert*-butyl-1-iodocyclohexene (**2**), α-iodostyrene (**3**) and 17-iodoandrost-16-ene (**4**) were aminocarbonylated in the presence of palladium catalysts formed *in situ* by the reaction of palladium(II) acetate and triphenylphosphine.[19–21] Two 1,1-disubstituted (cyclic) hydrazines, such as 3-amino-3-azabicyclo[3.3.0]octane (**a**) and (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP, **b**)/(*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP, **c**) (Scheme 1) were used as *N*-nucleophiles in DMF.

The aminocarbonylation of iodoalkenes (**1**–**4**) with **a** resulted in the high-yielding formation of the α,β-unsaturated hydrazide products (**1a**–**4a**) in all cases (Table 1). The reaction is highly chemoselective, no further products could be detected. The increase in carbon monoxide pressure had no influence on the selectivity, that is, no double carbon monoxide insertion leading to 2-ketocarboxamides took place (entries 3 and 5). Practically complete conversion was obtained in all cases in 4 h enabling facile isolation of the target products. The high reactivity of iodoalkenes (**1a-4a**) towards nucleophile **a** can be illustrated by the hydrazinocarbonylation of **1** providing conversion of 2%, 10%, 51% and 98% in 0.5 h, 1 h, 2 h and 4 h, respectively.

All products were isolated in high analytical purity (>98%) from reaction mixtures when the substrates were practically fully converted (Table 1). Good to excellent yields were obtained and the target compounds were fully characterised (See Experimental).

Similarly, carboxamides **1b**–**4b** or **1c**–**4c** were obtained exclusively when the above iodoalkene substrates, **1**–**4** were reacted with **b** (or **c**) under atmospheric carbon monoxide pressure (Table 2). As above, the reaction was practically complete in 4 h resulting in good to excellent isolated yields. As for the substrates, the only exception was **3**. In spite of the full conversion and good chemoselectivity, the isolation in high yields was unsuccessful.



Scheme 1. Hydrazinocarbonylation of iodoalkenes (**1**–**4**) in the presence of 3-amino-3-azabicyclo[3.3.0]octane (**a**) and SAMP (**b**) or RAMP (**c**) as *N*-nucleophile.

Table 1
Palladium-catalysed hydrazinocarbonylation of iodoalkenes (**1**–**4**) in the presence of 3-amino-3-azabicyclo[3.3.0]octane (**a**).[a]

Entry	Substrate	p(CO) [bar]	Isolated yield [%] (compound)
1	**1**	1	83 (**1a**)
2	**2**	1	69 (**2a**)
3	**2**	40	79 (**2a**)
4	**3**	1	54 (**3a**)
5	**3**	40	64 (**3a**)
6	**4**	1	53 (**4a**)

[a] Reaction conditions (unless otherwise stated): 1 mmol of substrate (**1**–**4**); 1.2 mmol of **a**; 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of PPh_3; 0.5 mL of triethylamine; 10 mL of DMF, 50 °C; 4 h.

Table 2
Hydrazinocarbonylation of iodoalkenes (**1**–**4**) in the presence of (*S*)-1-amino-2-methoxymethylpyrroplidine (SAMP, **b**)/(*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP, **c**).[a]

Entry	Substrate	Nucleophile	Isolated yield [%] (compound)
1	**1**	**c**	88 (**1c**)
2	**1**	**b**	80 (**1b**)
3	**2**	**c**	98 (**2c**)
4	**2**	**b**	88 (**2b**)
5	**3**	**c**	40 (**3c**)
6	**3**	**b**	39 (**3b**)
7	**4**	**c**	99 (**4c**)
8	**4**	**b**	84 (**4b**)
9[b]	**4**	**b/c**	88 (**4b**/**4c**)[c]

[a] Reaction conditions: 1 mmol of substrate (**1**–**4**); 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of PPh_3; 1.2 mmol of *N*-nucleophile (**b** or **c**); 0.5 mL of triethylamine; 10 mL of DMF, 50 °C; p(CO) = 1 bar, 4 h.
[b] 2.2 mmol of racemic **b/c** was used.
[c] The two epimers were obtained in a ratio of *ca.* 1/1.

When SAMP (or RAMP), *i.e.*, the enantiomerically pure hydrazine derivative was used, a 1/1 mixture of two diastereoisomers was formed in the hydrazinocarbonylation of the chiral substrate **2** applied always as a racemic mixture. On the other hand, the diastereoselectivity of the hydrazinocarbonylation was investigated using (*R/S*)-1-amino-2-methoxymethylpyrrolidine as racemate (**b**/**c** = 1/1). No diastereoselection was observed, that is, *ca.* a 1/1 mixture of the two diastereoisomers (**4a**/**4b**) were obtained in the presence of 2.2 equivalents of racemic 1-amino-2-methoxymethylpyrrolidine and **4** as a substrate (Table 2).

2.2. Hydrazinocarbonylation of iodobenzene in the presence of 3-amino-3-azabicyclo[3.3.0]octane as cyclic (1,1-disubstituted) hydrazine

As a comparison to iodoalkenes, the aminocarbonylation of iodobenzene (**5**) was carried out under similar conditions (Scheme 2). The detailed analysis of the reaction mixtures revealed that **5** is much less reactive than **1**–**4** in palladium-catalysed hydrazinocarbonylation and in general, rather complex mixtures can be obtained. In addition to the expected products, benzoic hydrazide (**5a**) and phenylglyoxylic hydrazide (**6a**) formed via mono and double carbon monoxide insertion, respectively, further types of side-products were identified. First, due to the relatively low reactivity of the substrate and the long reaction times, the *N,N*-dimethylbenzamide (**7**) and *N,N*-dimethylphenylglyoxylamide (**8**) were formed. Second, deamination of nucleophile **a** yielded the formation of two additional carboxamide and 2-ketocarboxamide-type products (**9** and **10**, respectively) containing the 3-azabicyclo[3.3.0] octane moiety only.

The formation of *N,N*-dimethylcarboxamide (**7**) and *N,N*-