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Synthesis of N-picolylcarboxamides in aminocarbonylation

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ABSTRACT

Palladium-catalysed aminocarbonylation of iodocamphene and steroidal iodoalkenes was carried out in the presence of 2-, 3- and 4-picolylamine, as well as secondary amines possessing 1-picolyl substituent. In general, primary picolylamines require less than 2 h to achieve practically complete conversion. The secondary amines proved to be less reactive, requiring 6–24 h depending on the substrate structure. The corresponding carboxamides were isolated in moderate to excellent yields. The synthesis of α,β-unsaturated carboxamides is based on the synthesis of iodoalkene substrates from enolizable ketones.

1. Introduction

Carboxamides, showing great variety in structures regarding both carboxylic acid and N-substituent moieties, belong to most investigated compounds due to their high practical importance [1]. In addition to widely known text-book reactions, homogeneous catalytic reactions opened a new avenue in synthetic chemistry due to their high chemo-, regio- and enantioselectivity [2]. Carboxamides of practical interest, *e.g.* those possessing steroidal backbones [3,4], have been synthesised using aminocarbonylation of enol triflates or their synthetic surrogates, iodoalkenes. It has to be noted that the above methodology is based on the seminal work of Heck *et al.* [5] Since the early discovery of palladium-catalysed aminocarbonylation of iodo- and bromoarenes, several reviews were also published regarding this topic [6].

The importance of the picolyl fragments, regarding their coordination properties [7] and biological effects [8], has already been shown by several publications. The efficiency of palladium-catalysed aminocarbonylation of iodoarene model substrates has already been shown for the synthesis of N-picolyl aromatic carboxamides [9].

There are several aspects of the application of N-picolylcarboxamides (Fig. 1). Isophthalic carboxamide derivatives with N-3-picolyl substituent have shown pharmacological activity in thromboembolitic disorders [10]. Picolylamide-based diselenides exhibited strong thiol peroxidase-like (TPx) activity [11]. Picolyl-substituted pyrido[1,2-a]-pyrimidine-3-carboxamides were evaluated as analgesic drugs [12].

Picolylcarboxamides were used also as ligands in transition metal complexes such as Cd [13], Cu [14], Zn [15] and Pd [16] and used for instance as chemical sensors and catalysts in Heck reaction.

In the present paper, a new procedure for the synthesis of unsaturated carboxamides (camphene- and steroid-based compounds) bearing N-picolyl substituents will be described. Iodoalkenes, available from the corresponding ketones via their hydrazones, were used as substrates.

2. Results and discussion

To investigate the formation of α,β-unsaturated carboxamides, the corresponding iodoalkenes such as iodocamphene (**1**), 17-iodoandrost-16-ene (**2**), 17-iodo-3-methoxy-estra-1,3,5(10),16-tetraene (**3**), 20-iodopregna-20-ene (**4**), 20-iodo-3β-hydroxypregna-5,20-diene (**5**) and 12-iodo-3β-hydroxyspirost-11-ene (**6**) were synthesised using the improved Barton's method [17]. In this way, the corresponding ketone was transferred to its hydrazone, and reacted further with iodine in the presence of base (triethylamine or N,N,N′,N′-tetramethylguanidine (TMG)) to furnish the

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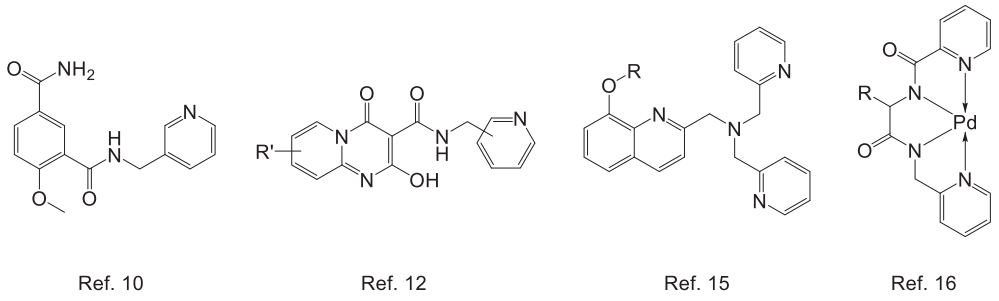


Fig. 1. N-Picolylcarboxamides of practical importance.

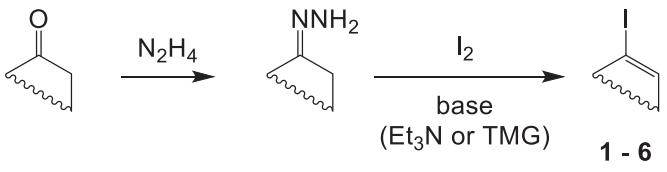
iodoalkene (Scheme 1) (See *Experimental*).

The iodoalkenes **1**–**6** were reacted as substrates in palladium-catalysed aminocarbonylation reaction (Scheme 2). Amines bearing picolyl substituents, such as primary (2-picolylamine (**a**), 3-picolylamine (**b**) and 4-picolylamine (**c**) and secondary amines (ethyl-4-picolylamine (**d**) and di-(2-picolyl)amine (**e**) were used as *N*-nucleophiles in DMF under atmospheric carbon monoxide in the presence of palladium(0)-triphenylphosphine catalysts formed *in situ*. These catalytic systems containing low-ligated palladium(0) species proved to be superior to 'preformed' palladium(0) complexes such as $Pd(PPh_3)_4$ due to their higher activity and easier chromatographic work-up of the reaction mixture. The formation of these coordinatively highly unsaturated Pd(0) species was investigated by cyclic voltammetry and NMR techniques [18].

The iodoalkene functionalities reacted selectively and quantitatively toward the corresponding α,β-unsaturated carboxamides possessing chiral backbones. Under the mild reaction conditions used (atmospheric CO pressure, 50 °C) no side-products were observed. All of the above isolated yields (Fig. 2) were obtained from reactions yielding the products in higher than 98% conversion. To achieve practically complete conversion, in most cases requires 1–2 h. Especially high reactivity was observed with substrate **1**, where even the secondary amine nucleophiles (**d,e**) required 2 h only. Much higher difference between primary and secondary amines have been observed with steroidal iodoalkenes. The use of primary amines (**a**,**b**,**c**) resulted in full conversion in less than 2 h in case of **2**, **3**, **4** and **6**, and even shorter reaction times (1 h) are necessary in case of **5**. The same trends but with longer reaction times can be observed with secondary amines (**d**,**e**): 24 h are required to convert substrates **3**,**4** and **6** to the corresponding carboxamides (**3d,e**; **4d,e** and **6d,e**, respectively), while only 6 h are necessary to obtain **2d,e**. The most reactive steroidal substrate **5** can be transferred to **5d** and **5e**, in 1 and 2 h, respectively.

Regarding chemoselectivity issues, the following statements can be done:

i) No double carbon-monoxide insertion resulting in 2-ketocarboxamides has been observed.
ii) Furthermore, under the mild conditions used, no ketone or alkene formation as side-reaction from the iodoalkene took place in hydrolysis or hydrogenolysis, respectively.



Scheme 1. A general scheme for the synthesis of iodoalkenes.

iii) The aminocarbonylation tolerates functional groups, for instance 3β-hydroxy groups of **5** and **6.** No elimination of water providing the corresponding diene or alkene, respectively, has been observed.

3. Conclusions

As a summary it can be stated, that new N-picolyl-carboxamides can be synthesised by the functionalization of chiral backbones in moderate to excellent yields in palladium-catalysed aminocarbonylation. The highly selective reaction is based on the availability of the corresponding iodoalkenes from enolizable ketones such as camphor and steroidal ketones.

4. Experimental

4.1. Chemicals, general procedures

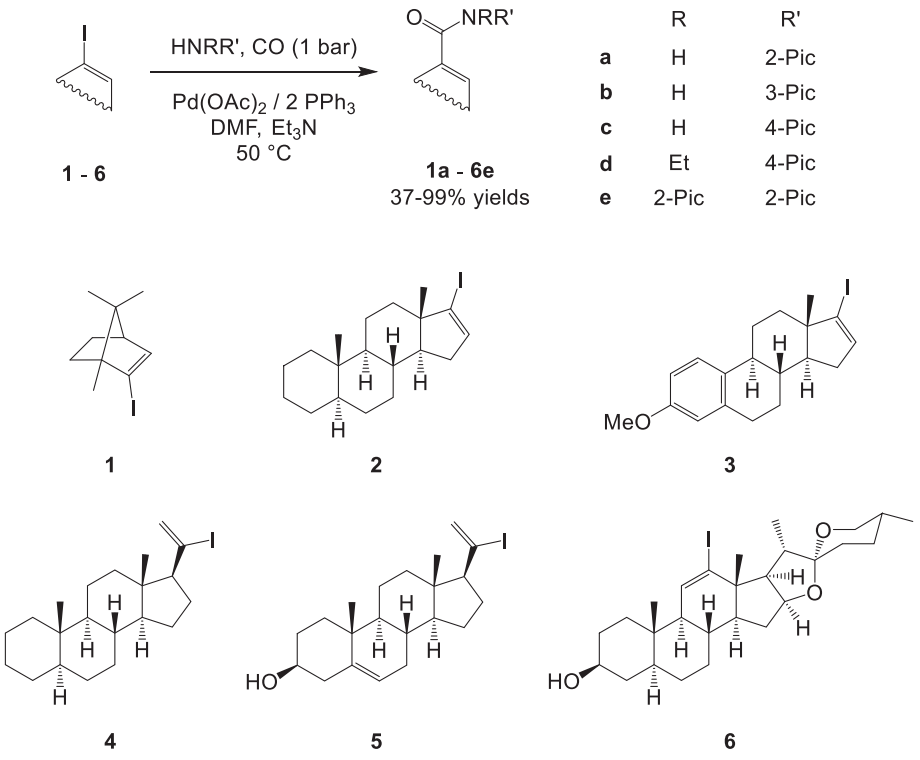
PPh_3, palladium(II) acetate were purchased from Sigma-Aldrich. Commercial Et_3N, primary and secondary amines including amino acid esters (Sigma-Aldrich) were used without further purification. Toluene and DMF were dried according to standard procedures; THF, ethyl acetate and ethanol were used without further purification.

The iodoalkene substrates (**1** [19], **2** [20], **3** [21], **4** [22], **5** [22b] and **6**[23]) were synthesised as described before.

The ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer at 500 and 125.721 MHz, respectively. The chemical shifts are given as δ values (ppm) and referenced to tetramethylsilane. TLC analyses were carried out by using Merck TLC sheets (Silica gel 60 F_{254}) and chloroform, chloroform/ethyl acetate, and chloroform/methanol mixtures were used as appropriate eluents. (The exact ratios are given at the corresponding synthetic procedures.) Mass-spectrometry data have been obtained by using a GC-MS system consisting of a PerkinElmer AutoSystem XL gas-chromatograph and PerkinElmer TurboMass mass spectrometer or LC-MS system Agilent 1290 Infinity UHPLC with Zero Dead Volume unit and Agilent 6530 QTOF mass spectrometer, eluent: methanol (0,1 v/v % formic acid).

4.2. General procedure for aminocarbonylation at atmospheric pressure

An iodoalkene **1** (or **2**–**6**) (1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol), and PPh_3 (13.1 mg, 0.05 mmol) were dissolved in 10 mL DMF under argon. Triethylamine (0.5 mL) and 2-picolylamine (**a**) (0.206 mL 2 mmol) (or another picolylamine *N*-nucleophile 2 mmol (**b**-**e**)) were added. The atmosphere was changed to CO (1 bar), and the reaction was conducted at 50 °C for the appropriate reaction time. The composition of the reaction



Scheme 2. Synthesis of carboxamides (**1a**-**6e**) in palladium-catalysed aminocarbonylation.

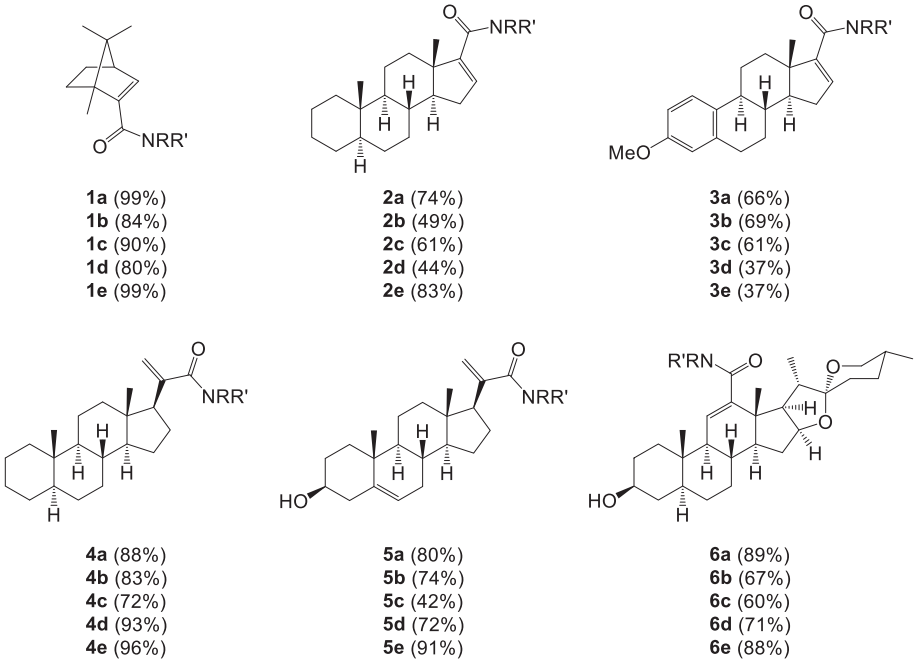


Fig. 2. Isolated yields (conversion higher than 98% in all cases) obtained in aminocarbonylation of iodoalkenes **1**–**6** (2.5% $Pd(OAc)_2$, 5% PPh_3, 0.5 mL of Et_3N, 1 bar CO, solvent: DMF, 50 °C, reaction time: 1–24 h (for details see discussion below)).

mixture was checked by GC (or TLC). The solvent was evaporated, and the residue was dissolved in 20 mL of $CHCl_3$. It was washed in turn with 20 mL of water and brine. The organic layer was separated, dried over Na_2SO_4 and evaporated. Column chromatography (silica gel, 95/5, 90/10 $CHCl_3$ MeOH; the exact mixtures are given in Supporting Information) resulted in the target chiral α,β-unsaturated carboxamides (**1a**-**e**, **2a**-**e**, **3a**-**e**, **4a**-**e**, **5a**-**e** and **6a**-**e**).

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132128.

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