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ORIGINAL PAPER

Synthesis of novel pregnane-based 20-carboxamides via palladium-catalysed aminocarbonylation

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Abstract

20-Carboxamidopregnene derivatives, such as 3β-acetoxy-5α-pregn-20-ene-20-carboxamides and 5α-pregn-20-ene-20-carboxamides were synthesized from the widely accessible 3β-acetoxy-pregn-5,16-dien-20-one (PDA) using selective hydrogenation, hydrazine and iodoalkene formation, as well as palladium-catalysed aminocarbonylation. The 20-iodo-20-ene derivatives, obtained from the corresponding 20-keto derivatives via their hydrazones, served as substrates. 23 new 20-carboxamides were obtained using various *N*-nucleophiles ranging from simple primary amines to α-amino acid esters. The novelty of this methodology lies in the application of facile, moderate or high-yielding reactions to obtain otherwise hardly accessible steroidal 20-carboxamides of pharmaceutical importance. In other words, instead of the enzymatic or synthetic degradation of e.g., sterols or cholanic acids, functionalization of the basic skeleton (a 'building-up' approach) was used.

Keywords Iodoalkene · Carboxamide · Pregnane · Palladium · Aminocarbonylation

Introduction

The efficiency of homogeneous catalytic reactions, due to their high activity, as well as chemo-, regio- and enantioselectivity is well known. In the last decades the highly selective hydrogenation, isomerization, various carbonylation and cross-coupling reactions, catalysed by various transition metal complexes, have become important tools of the synthetic chemist.

Among the homogeneous catalytic functionalization of various skeletons of practical importance (Cornils et al. 1996; Beller et al. 1998; Omae 1998), that of the steroidal backbone is of primary interest (Skoda-Földes et al. 2003). A great variety of transition metal-catalysed reactions, for instance alkene and carbonyl hydrogenations, various carbonylations and coupling reactions were used to introduce new functionalities. Among these reactions, the synthesis of carboxamides via palladium-catalysed aminocarbonylation is one of the most promising one. Several families of these steroid-based carboxamides possess 5*a*-reductase inhibitor properties (see below).

The synthesis of carboxamides from easily available iodoaromatics (or aryl triflates, their synthetic surrogates) is a straightforward methodology. The seminal work of Heck et al. ('Heck-carbonylation') (Schoenberg and Heck 1974a, b, Schoenberg et al. 1974) provided a solid

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basis for the homogeneous catalytic functionalization of the above substrates. Several reviews and book chapters have been published on the aminocarbonylation of aryl halides (Roy et al. 2012; Wu et al. 2011, 2013; Magano and Dunetz 2011; Grigg and Mutton 2010; Barnard 2008; Skoda-Földes et al. 2002; Gadge and Bhanage 2014). Even the importance of the double carbon monoxide insertion resulting in 2-ketocarboxamides (Ozawa et al. 1984; Son et al. 1988) has been emphasised, i.e., the chemoselectivity towards 2-ketocarboxamides/carboxamides is an important issue. However, the aminocarbonylation of iodoalkenes/enol triflates is a chemoselective reaction providing unsaturated carboxamides only (Kiss et al. 2015). The double carbon monoxide insertion, i.e., the formation of unsaturated ketocarboxamides requires special triarylphosphite-based palladium catalysts (Carrilho et al. 2012).

The introduction of an amide functionality in steroidal substrates via palladium-catalysed aminocarbonylation, especially into the most distinguished position-3 and -17 (in ring A and D, respectively), has long been the aim of the patent literature as well (Holt et al. 1989, 1990; Cacchi et al. 1986; Dolle et al. 1987; Tian et al. 2000; McGuire et al. 1998; Petz et al. 2001). Efforts have been made also for the synthesis of 11- and 12-carboxamides using the same methodology, i.e., aminocarbonylation of the corresponding iodoalkene functionalities in the most hindered positions (Ács et al. 2006, 2007). Although the pharmacological importance such as inhibition of concise enzymes in ergosterol biosynthesis (Müller et al. 2015), anti-inflammatory (Kim et al. 1987), 24-methyl transferase (Lorente et al. 2005) and anti-microbial activities (Khabnadideh et al. 2000) of 20-carboxamides have been reported, to the best of our knowledge, only cholenic acid-based multistep procedures have been published for their synthesis. The procedure includes the activation of 20-acids as nitrophenol esters, followed by protection-deprotection sequence. Alternatively, ergosteryl acetate has been subjected to hydrogenation using Raney Ni, and the 5α,6-dihydroergosteryl acetate product has been oxidized to the corresponding acid using potassium permanganate. The acid chloride has been prepared by oxalyl chloride and reacted further with the corresponding primary or secondary amine (Giera et al. 2008).

Based on our preliminary investigations with similar iodoalkene functionalities, i.e., their use in aminocarbonylation/cyclization sequence to obtain oxazoles (Szuroczki et al. 2018), as well as in asymmetric aminocarbonylation to obtain diastereoisomers of various carboxamides (Mikle 2017), a systematic investigation regarding the structure of both substrate and *N*-nucleophile was decided. In the present paper, a facile procedure for the synthesis of 20-carboxamidopregnenes is described using the 20-keto—20-hydrazone—20-iodo-20-ene—20-carboxamido-20-ene reaction pathway.

Experimental

Materials and equipment

Celite®, sodium hydroxide, iodine, PPh_3, palladium(II) acetate, PDA (**1**) and Pd/C catalyst 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 ^{1}H- 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 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 using a GC–MS system consisting of a Perkin Elmer AutoSystem XL gas-chromatograph and Perkin Elmer TurboMass mass spectrometer.

Hydrogenation of 1 and 4

The unsaturated steroid 3β-acetoxy-pregn-5,16-diene-20-one ('PDA') (**1**) (or in the analogous procedure, **4**) (20 g, 56.1 mmol) was dissolved in ethyl acetate (120 mL) under argon in a 500 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon at the top. A suspension of 605 mg of Pd/C (5%) (or 605 mg of Pd/C (10%)) in ethyl acetate (20 mL) was added to the stirred solution at room temperature, then the atmosphere was changed to H_2 (1 bar). The composition of the reaction mixture was checked by GC. After completion of the reaction, the mixture was filtered on Celite®. The solvent was removed and the product was recrystallized from ethyl acetate. Yield: **2**: 18.04 g (90%) (when Pd/C (5%) was used); **3**: 17.3 g (85%) (when Pd/C (10%) was used).

Synthesis of 4 via hydrolysis and water elimination

The compound saturated in both 5-ene and 16-ene positions (**3**) (8.5 g, 23.67 mmol) was dissolved in 240 mL of ethanol and 10% NaOH solution (6.3 mL) was added. The reaction mixture was heated for 2 h at 100 °C then concentrated under reduced pressure. Coldwater (200 mL) and 10% HCl solution (20 mL) were added. The steroid was filtered and washed with water to neutral pH, and dried.

The hydrolysed steroid (7.3 g, 22.92 mmol), *p*-toluenesulfonic acid monohydrate (1.75 g, 9.22 mmol) and silica

gel (52.64 g) were dissolved in toluene (460 mL) and stirred at 120 °C for 5 h. The composition of the reaction mixture was checked by GC. After the reaction was completed, the silica was filtered off, washed with toluene (1000 mL) and the solvent was evaporated. Yield: 4.82 g (70%).

Synthesis of 20-iodo-3β-acetoxy-5α-pregn-20-ene (8) and 20-iodo-5α-pregn-20-ene (9)

3β-Acetoxy-pregn-5-ene-20-one (**2**) or 5α-pregnan-20-one (**5**) (14 mmol), hydrazine hydrate (15.2 mL, 314 mmol) and triethylamine (7.8 mL, 55.8 mmol) in ethanol (42 mL) were stirred for 2.5 h at 100 °C under argon. After cooling, removal of the solvent resulted in some crystal formation. Coldwater (100 mL) was added to the mixture. The precipitated material was filtered and washed with water to neutral pH. The white crystalline hydrazone (**6**, **7**) was dried to constant weight under vacuum.

The hydrazone (**6**) (or **7**) (13.46 mmol) and triethylamine (18.8 mL, 134.6 mmol) were dissolved in THF (87 mL) under argon in a 500 mL three-necked flask. A solution of iodine (6.84 g, 26.92 mmol) in THF (26 mL) was added dropwise to the stirred solution. After the addition was completed, the mixture was stirred for 1 h. The amine salt was filtered and the mixture was poured dropwise into a stirred solution of $Na_2S_2O_5$ (7.06 g, 37.14 mmol) in water (1000 mL). The precipitated steroid was filtered and washed with water to neutral pH and dried under vacuum. The steroidal iodoalkene was recrystallized from aqueous ethanol.

General procedure for aminocarbonylation

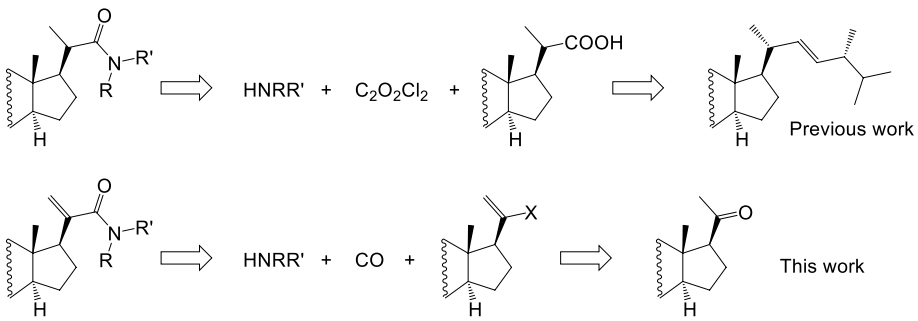
A steroidal iodoalkene substrate **8** (or **9**) (1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol), and PPh_3 (13.1 mg, 0.05 mmol) were dissolved in 10 mL DMF under argon. Triethylamine (0.5 ml) and *tert*-butylamine (**a**) (0.525 mL 5 mmol) [or another *N*-nucleophile 1.5 mmol (**b**–**e**)] were added. (The amino acid methyl esters (**f**–**k**) were used as hydrochloride salts (1.1 mmol) and were added together with the catalyst.) 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 mixture was checked by GC. 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, 20 mL portions of 5% HCl, saturated $NaHCO_3$, and brine. The organic layer was separated, dried over Na_2SO_4 and evaporated. Column chromatography (silica gel, 95/5 $CHCl_3$/MeOH, 100/0, 95/5, 90/10, 80/20, or 50/50 $CHCl_3$/EtOAc; the exact composition of the eluents are given in Supporting Material) resulted in the target 20-carboxamido-20-ene derivatives (**10a-k**, **11a-l**).

Results and discussion

Synthesis of 20-iodo-20-ene derivatives from PDA

According to a retrosynthetic analysis (Scheme 1), to synthesize steroids with carboxamido functionality at the position-20, pregnene derivatives possessing the 20-iodo/trifiloxy-20-ene moieties have to be obtained. To achieve this goal, one of the most efficient ways could be the synthesis of the corresponding 20-keto derivatives. In contrary to previous approaches based on the degradation of sterols (for instance Giera et al. 2008), our methodology is aimed at using functionalization of a pregnane skeleton. Although the oxidative degradation approach, i.e., the oxidation of the C_8–C_{10} alkenyl chains bound to 17-position, has been used to obtain pregnane- and androstane-based compounds for a long time (Giera et al. 2008, Fried et al. 1972), the high chemoselectivity (practically no steroidal side products) and the simple protocol encouraged us to follow the 'bottom-up' approach based on 20-keto derivatives. Furthermore, the synthesis is based on the application of simple 'small molecules', such as carbon monoxide and primary and secondary amines as building blocks.

3β-Acetoxy-pregn-5,16-diene-20-one (pregna-5,16-dien-3β-ol-20-one acetate, 'PDA') (**1**) was chosen as starting material. Its heterogeneous catalytic hydrogenation (Scheme 2) leads to the partially and fully hydrogenated compounds, **2** and **3** (Shingate et al. 2007), respectively. The hydrogenation of the double bonds proceeds in a consecutive manner, therefore, both compounds (**2** and **3**) possessing the required 20-keto functionalities can be obtained



Scheme 1 Retrosynthetic analysis of the synthesis of steroidal 20-carboxamides. (R,R′: H, alkyl, aryl; X: I, OTf)

as analytically pure compound. The hydrogenation of both 16-ene and 5-ene double bonds are highly stereoselective: 17α-H and 5α-H epimers were obtained with high selectivity. As expected, heterogeneous hydrogenation takes place preferably from the α-side.

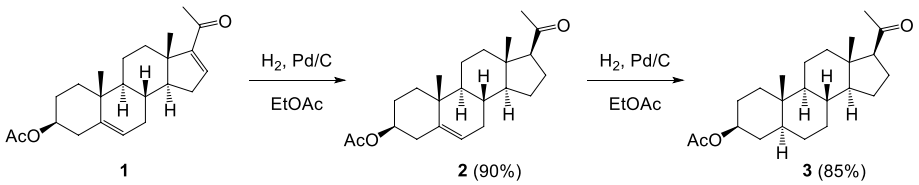
To synthesize a model compound without 3β-acetoxy functionality, two pathways were chosen: (1) acetic acid was eliminated from compound **1**, and the resulting mixture of dienes (3,5-diene and 2,4-diene) was hydrogenated to the hardly separable mixture of the two epimers (5α- and 5β-prenan-20-one formed mainly from 3,5-diene and 2,4-diene, respectively); (2) the pure 5α-epimer (**3**) was subjected to acetate hydrolysis and elimination of water (D'Onofrio and Scettri 1985), and the hydrogenation of the mixture of 2-ene and 3-ene (**4**) resulted in the formation of **5** (Scheme 3). Since the first methodology proved to be not feasible, in further syntheses, the latter method, resulting in practically epimerically pure product (**5**) was applied.

The 20-iodo-20-ene substrates **8** and **9** were synthesised from the corresponding ketones (**2** and **5**) via their hydrazones (**6** and **7**, respectively), using the modified Barton's method (Scheme 4) (Barton et al. 1962, 1983, Krubine et al. 1969).

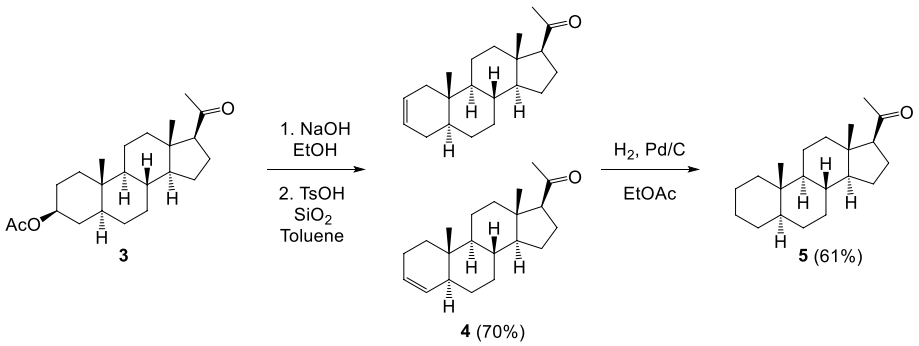
Synthesis of 20-carboxamido-20-enes via palladium-catalysed aminocarbonylation

The iodoalkenes **8** and **9** were reacted as substrates in palladium-catalysed aminocarbonylation reaction (Scheme 5). Various primary and secondary amines were used as *N*-nucleophiles (*tert*-butylamine (**a**), aniline (**b**), benzylamine (**c**), piperidine (**d**), morpholine (**e**), methyl glycinate (**f**), methyl alaninate (**g**), methyl serinate (**h**), methyl valinate (**i**), methyl phenylalaninate (**j**), methyl prolinate (**k**)) and α-phenylethylamine (l) in DMF under atmospheric carbon monoxide in the presence of

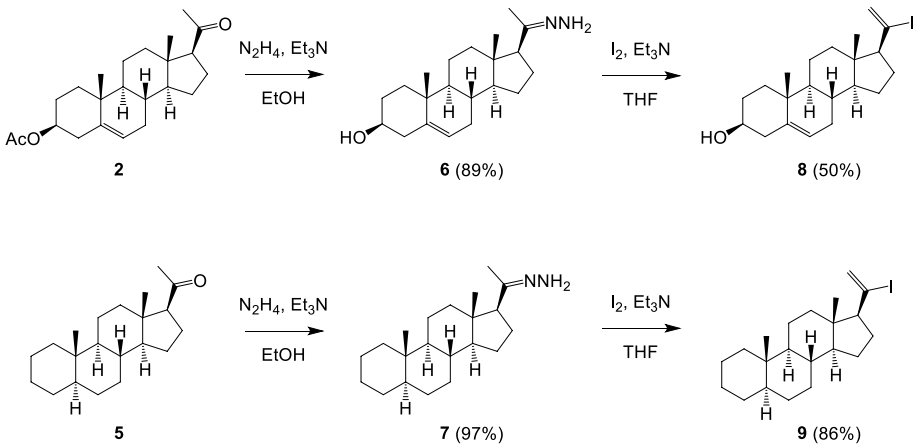
Scheme 2 Hydrogenation of **1**

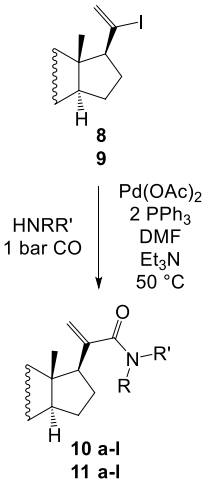


Scheme 3 The synthesis of 5α-pregnan-20-one (**5**)



Scheme 4 Synthesis of 20-iodo-20-ene derivatives (**8**, **9**)





	R	R'
a)	H	^{t}Bu
b)	H	Ph
c)	H	CH_2Ph
d)	-$(CH_2)_5$-	
e)	-$(CH_2)_2$-O-$(CH_2)_2$-	
f)	H	CH_2COOCH_3
g)	H	$CH(CH_3)COOCH_3$
h)	H	$CH(CH_2OH)COOCH_3$
i)	H	$CH(CH(CH_3)_2)COOCH_3$
j)	H	$CH(CH_2Ph)COOCH_3$
k)	-$CH(COOCH_3)(CH_2)_3$-	
l)	H	$CH(CH_3)Ph$

Scheme 5 Aminocarbonylation of iodoalkenes (**8**, **9**) toward 20-carboxamides (**10**, **11**)

Table 1 Isolated yields of 20-carboxamides (**10a–l** and **11 a–l**)[a]

N-nucl	Products [isolated yields, (%)]	
a	**10a** (75)	**11a** (52)
b	**10b** (51)	**11b** (51)
c	**10c** (97)	**11c** (51)
d	**10d** (56)	**11d** (51)
e	**10e** (63)	**11e** (53)
f	**10f** (49)	**11f** (39)
g	**10g** (43)	**11g** (41)
h	**10h** (59)	**11h** (54)
i	**10i** (33)	**11i** (55)
j	**10j** (54)	**11j** (51)
k	**10k** (59)	**11k** (50)
l	**10l** (92)[b]	**11l** (75)

[a]For reaction conditions see "General procedure for aminocarbonylation" (above)

[b]Mikle et al. 2017

palladium(0)-triphenylphosphine catalysts formed in situ. Palladium(II) acetate was used as a catalytic precursor.

The formation of highly active coordinatively unsaturated Pd(0) species was investigated by cyclic voltammetry and NMR techniques in the presence of mono- and bidentate phosphines (Csákai et al. 1999, Amatore et al. 1992, 1995). It has to be noted that triphenylphosphine was used only in a twofold excess to palladium. One equivalent is responsible for the reduction of Pd(II) to Pd(0) while it is oxidised to triphenylphosphine oxide.

The resulting Pd(0) intermediate is a highly reactive, low-ligated intermediate which is apt to activate the iodoalkenyl substrates (**8**, **9**) in oxidative addition. This type of catalytic system proved to be efficient also in further steps of the catalytic cycle such as carbon monoxide activation, its insertion into the alkenyl-palladium bond, amine activation, as well as reductive elimination in the product-forming step (Table 1).

The iodoalkene functionality (20-iodo-20-ene) reacted selectively and quantitatively toward the corresponding 20-carboxamido-21-ene derivatives (**10a–k**, **11a–l**) under mild conditions (atmospheric CO pressure, 50 °C). As expected, practically no influence of the structure of the A-ring on conversion and isolated yields was observed. That is, the removal of 3β-hydroxy functionality has no measurable effect on the reactivity of the 20-iodo-20-ene moiety.

However, the structure of the amine nucleophile has some effect on the conversion. In general, 1–1.5 h are needed to achieve close to complete conversion ('GC-yields' higher than 98%). In the case of **b**, **d, e** and **k** nucleophiles 3 h, 5 h, 4.5 h and 4 h reaction times were requested, respectively. The low reactivity of the less basic aromatic amine (**b**) is not surprising in the light of earlier results obtained with a great variety of iodoalkenes. In general, the secondary amines, especially **k** show lower reactivity than the primary amines (Schoenberg and Heck 1974a, b, Schoenberg et al. 1974, Skoda-Földes et al. 2002, Kiss et al. 2015). Using these steroidal iodoalkene substrates (20-iodo-20-pregnenes) this effect is even more pronounced.

As mentioned above, the reactions were conducted to almost complete conversion. In spite of that, the isolated yield of the target carboxamides can be considered as moderate only, due to the loss of products during chromatographic work-up of the catalytic reaction mixture. In this way, the isolated yields of the analytically pure products varied from 33 to 97%. In general, the carboxamides **10** can be isolated in higher yields than carboxamides **11** (compare for instance **10a** and **11a**; **10c** and **11c**; **10e** and **11e**, etc.). As the only exception nucleophile **i** has to be mentioned, i.e., **11i** was isolated in higher yield than **10i**.

Conclusions

In conclusion, it can be stated, that pregnane skeletons functionalised at 20-position can be synthesized in yields of practical interest in palladium-catalysed aminocarbonylation. 20-Iodo-20-ene functionality, easily accessible from 20 to one, provided a clean, high-yielding aminocarbonylation towards 20-carboxamido compounds. Although the reactivity of the amines depends on their basicity, even with less basic aromatic amines and more bulky ones isolated yields of practical importance can be obtained.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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