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Facile, High-yielding Synthesis of Steroidal Hydrazides via Homogeneous Hydrazinocarbonylation Reaction

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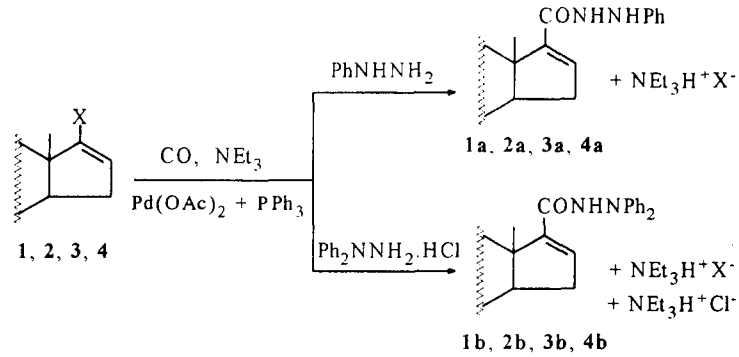
Abstract: 17-(N-(phenylamino)-carbamoyl)-androst-16-enes were synthesised in high yields in palladium-catalysed hydrazinocarbonylation of the corresponding 17-iodo-androst-16-ene derivatives under mild reaction conditions. © 1997 Elsevier Science Ltd.

The recognition of the importance of the 5α-dihydrotestosterone (DHT)-level in many diseases has stimulated efforts to synthesize inhibitors of 5α-reductase, which is an NADPH-dependent enzyme that converts testosterone to DHT. In addition to steroidal carboxylic acids [1], secosteroids [2] and diazaketone steroids [3], 17-carboxamido-androstanes (*eg.* 17β-N-*tert*-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one (MK-906), Finasterid [4]) have been shown to be efficient inactivators of this enzyme. Palladium-catalysed carbonylation of the corresponding enol-triflates proved to be a very efficient reaction for the synthesis of steroidal amides [5-8].

The preparation of 17β-(N-(diarylmethyl)-carbamoyl)-androstane and 17β-(N-(arylmethyl)-carbamoyl)-androstane derivatives as novel classes of 5α-reductase inhibitors have been reported, recently [9].

In the present paper, we report a highly efficient novel synthesis of 17-(N-(phenylamino)-carbamoyl)-androst-16-enes (the aza-analogue of the above derivatives) *via* palladium-catalysed homogeneous hydrazinocarbonylation of the corresponding 'iodo-vinyl' ('bromo-vinyl') androstanes bearing 17-iodo-16-ene or 17-bromo-16-ene functionalities [10]. To the best of our knowledge, this homogeneous catalytic method is unprecedented even for the synthesis of simple hydrazides.

17-Iodo-androsta-16-ene (**1**), 17-iodo-4-aza-androsta-16-en-3-one (**2**), 17-iodo-4-aza-4-methyl-androsta-16-en-3-one (**3**) and 17-bromo-androsta-2,16-diene (**4**) were reacted with carbon monoxide and phenylhydrazine or 1,1-diphenylhydrazine hydrochloride in the presence of palladium(II) acetate, triphenylphosphine and triethylamine. The corresponding 17-(N-(phenylamino)-carbamoyl)- and 17-(N-diphenylamino)-carbamoyl)-androsta-16-enes were obtained in high isolated yields (74—82% isolated yields, except for **4**, where the yields were typically 30—35%). On the basis of TLC and NMR measurements the hydrazinocarbonylation reaction is practically complete under the given mild reaction conditions.



The acylation occured exclusively on the unsubstituted nitrogen. The reactive palladium-acyl intermediate, formed by oxidative addition of the substrate and subsequent carbon monoxide insertion into the palladium—carbon-17 bond, acylated the more nucleophilic center (the unsubstituted nitrogen). The dehydroiodation of the hydrido-iodo-palladium(II) intermediate by triethylamine furnishes the highly reactive, coordinatively unsaturated palladium(0) species which is able to activate the substrate by oxidative addition.

A typical experiment is as follows. A mixture of an 'iodo-vinyl' derivative (1 mmol), palladium(II) acetate (11.2 mg, 0.05 mmol), triphenylphosphine (26.2 mg, 0.1 mmol), triethylamine (0.5 ml), phenylhydrazine (0.5 ml, 5 mmol) (Method A) (or triethylamine (1 ml), diphenylhydrazine hydrochlorid (550 mg, 2.5 mmol) (Method B)) and dimethylformamide (15 ml) was heated under a carbon monoxide atmosphere (balloon filled with carbon monoxide at atmospheric pressure) at 60 °C. The reaction was followed by GC and TLC. It was complete usually within 3 hours. Some metallic palladium was formed at the end of the reaction which was filtered off. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (35 ml) and washed twice with water (35 ml). The organic phase was thoroughly washed, twice with 5% HCl (30 ml), than with saturated $NaHCO_3$ (30 ml) and brine (30 ml), dried over Na_2SO_4 and concentrated to a thick red oil (when **1** and **4** were used as substrates) or a yellow powder (in the case of **2** and **3**). Chromatography (silica, chloroform) yielded the desired compounds as white or pale yellow solids.

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