# Synthesis of N-Substituted Steroidal Hydrazides in Homogeneous Catalytic Hydrazinocarbonylation Reaction

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## Introduction

The various homogeneous catalytic carbonylation reactions (aminocarbonylation, alkoxycarbonylation) of iodoalkenes and enoltriflates in the presence of "preformed" and in situ palladium catalysts are widely used synthetic methods for the synthesis of compounds of practical importance.[1]

Among these reactions, the functionalization of various steroidal skeletons plays an important role. Since in addition to steroidal carboxylic acids,[2] secosteroids,[3] and diazaketone steroids,[4] some 17-carboxamidoandrostanes (e.g., 17*β*-(*N*-*tert*-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one (MK-906, Finasterid[5]) proved to be efficient 5α-reductase inhibitors, efforts were made toward the synthesis of inhibitors of this NADPH-dependent enzyme that converts testosterone to dihydrotestosterone (DHT). Palladium-catalyzed aminocarbonylation of the corresponding steroidal enol triflates proved to be a very efficient method for the synthesis of steroidal amides possessing high 5α-reductase inhibitor activity.[6−9]

Despite the above results, to the best of our knowledge, no homogeneous catalytic method is known either for the synthesis of simple hydrazides or hydrazides of pharmacological importance.

The present work was also encouraged by a recent paper on the preparation of 17*β*-(*N*-(diarylmethyl)carbamoyl)androstane and 17*β*-(*N*-(arylmethyl)carbamoyl)-androstane derivatives (Figure 1) as novel classes of 5α-reductase inhibitors.[10] The various 17-(*N*-(alkylamino)-carbamoyl)androst-16-enes and 17-(*N*-(arylamino)carbamoyl)androst-16-enes, which will be discussed in this paper, can be considered as the aza analogues of the aforementioned 17-carboxamidoandrostanes of pharmacological importance.

We report here the optimal conditions of the highly efficient novel synthesis of steroidal hydrazides in palladium-catalyzed homogeneous hydrazinocarbonylation.

## Results and Discussion

17-Iodoandrost-16-ene (**1**), 17-iodo-4-azaandrost-16-en-3-one (**2**), 17-iodo-4-aza-4-methylandrost-16-en-3-one (**3**), 17-iodo-6α-hydroxy-3α,5α-cycloandrost-16-ene (**4**), and 17-bromo-androst-2,16-diene (**5**) (Figure 2) were reacted with carbon monoxide and mono- or disubstituted hydrazines (phenylhydrazine, 1,1-diphenylhydrazine, methylhydrazine, 1,1-dimethylhydrazine) in the presence of palladium(II) acetate, triphenylphosphine and triethylamine (Scheme 1). The corresponding 17-(*N*-phenylaminocarbamoyl)- (**1a**−**5a**), 17-(*N*-diphenylaminocarbamoyl)- (**1b**−**4b**), 17-(*N*-amino-*N*-methylcarbamoyl)- (**1c**, **3c**−**5c**), and 17-(*N*-(dimethylamino)carbamoyl)androst-16-enes (**1d**, **3d**) were obtained in high isolated yields (Table 1). The hydrazinocarbonylation reaction was found to be practically complete in most cases under the given mild reaction conditions when the iodo substituent served as a leaving group. In the case of the 17-bromo-16-ene moiety (**5**), the yields are substantially lower, while with 1,1-diphenylhydrazine the desired product was obtained only in traces.

All of the reactions were highly regioselective; i.e., the steroidal hydrazides were obtained as single isomers. No side products were observed under standard reaction conditions (see the Experimental Section). All of the products were characterized by $^{1}$H and $^{13}$C NMR, MS, and IR. However, hydrazinocarbonylation was found to be a minor carbonylation reaction when the steroidal alkenyl iodide was used in excess compared to the hydrazine. In this case, the palladium−steroidal acyl complex reacted mainly with the water impurity furnishing a steroidal carboxylic anhydride.[11]

No diacylation has been observed either with mono- or disubstituted hydrazides. This can be explained by the fact that hydrazines were used in excess. Besides, the hydrazide that formed during the reaction is less nucleophilic than the hydrazine reagent itself. The high selectivity of acylation is surprising on the basis of the reactivity−selectivity principle, since such high regioselectivities (high differentiation toward acylation on more nucleophilic nitrogen) are expected for less reactive acylation reagents than a palladium−acyl intermediate. (This highly reactive complex is formed by oxidative addition of the steroidal iodoalkene onto the "in situ" formed palladium(0) species followed by carbon monoxide

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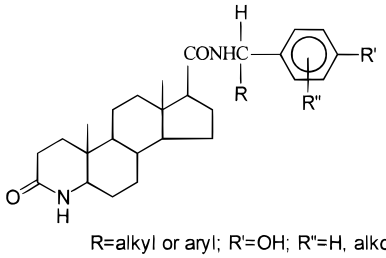



**Figure 1.** 17$\beta$-(*N*-(arylmethyl)carbamoyl)androstane derivatives of practical importance (ref 10).

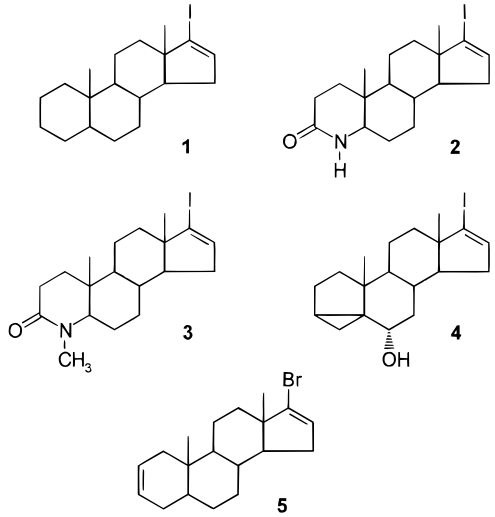
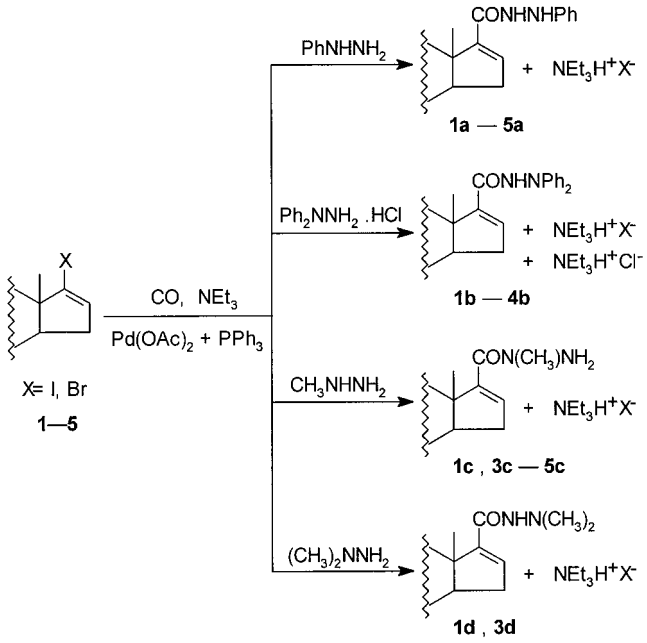



**Figure 2.** 17-Iodo(bromo)androst-16-enes used as substrates in the homogeneous catalytic hydrazinocarbonylation reaction.

**Scheme 1. Homogeneous Catalytic Hydrazinocarbonylation of 17-Iodo(bromo)androst-16-ene Derivatives in the Presence of Palladium Catalysts**




insertion into palladium−carbon bond.) Both electronic and steric factors favor the acylation in the more basic and less hindered 2-position when phenylhydrazine was used.

**Table 1. Palladium-Catalyzed Hydrazinocarbonylation of Steroids 1−5[a]**

| substrate | hydrazine | product | reaction time (h) | conversion[b] (%) | yield[c] (%) |
|---|---|---|---|---|---|
| **1** | $PhNHNH_2$ | **1a** | 3 (1) | >98 (80) | 83 |
| **1** | $Ph_2NNH_2$ | **1b** | 8 (1) | 60 (27) | 52 |
| **1** | $CH_3NHNH_2$ | **1c** | 3 (1) | >98 (87) | 85 |
| **1** | $(CH_3)_2NNH_2$ | **1d** | 3 (1) | >98 (65) | 82 |
| **2** | $PhNHNH_2$ | **2a** | 6 | >98 | 93 |
| **2** | $Ph_2NNH_2$ | **2b** | 8 | 96 | 77 |
| **3** | $PhNHNH_2$ | **3a** | 6 | >98 | 94 |
| **3** | $Ph_2NNH_2$ | **3b** | 8 | 95 | 66 |
| **3** | $CH_3NHNH_2$ | **3c** | 6 | >98 | 75 |
| **3** | $(CH_3)_2NNH_2$ | **3d** | 6 | 94 | 62 |
| **4** | $PhNHNH_2$ | **4a** | 6 | >98 | 94 |
| **4** | $Ph_2NNH_2$ | **4b** | 8 | >98 | 77 |
| **4** | $CH_3NHNH_2$ | **4c** | 6 | >98 | 87 |
| **5** | $PhNHNH_2$ | **5a** | 8 | 30 | 22 |
| **5** | $Ph_2NNH_2$ | **5b** | 8 | 10 | |
| **5** | $CH_3NHNH_2$ | **5c** | 8 | 35 | 27 |

[a] Reaction conditions: 1 mmol of steroid, 0.05 mmol of $Pd(OAc)_2$, 0.1 mmol of $PPh_3$, 0.05 mmol of $Et_3N$, 15 mL of DMF (solvent), CO atmosphere, 60 °C. [b] Determined by $^1H$ NMR on the basis of the integrals of the corresponding 16-H protons. [c] Isolated yields after the standard workup of the reaction mixture (see the Experimental Section).

In the case of methylhydrazine, acylation takes place exclusively on the N-Me nitrogen, despite the presence of the sterically hindered steroidal acyl−palladium intermediate. The regioselectivity of palladium-catalyzed homogeneous hydrazinocarbonylation seems to be controlled mainly by the substituent(s) of the hydrazine reagent, resulting in a substantial difference between the basicities of the two nitrogen atoms,[12] rather than the bulkiness of the acylation reagent.

The reactivities of the above hydrazines were compared by using **1** as substrate. Methylhydrazine was found to be the most reactive reagent. An 87% conversion was obtained in 1 h. In this case, the substituted nitrogen is more nucleophilic than any NH or $NH_2$ nitrogen of the other hydrazine derivatives because of the +I effect of the methyl group. Surprisingly, the acylation on the $NH_2$ of phenylhydrazine seems to be favored to that of 1,1-dimethylhydrazine. The corresponding steroidal hydrazides were formed in 80% and 65% yields in 1 h, respectively. This observation is not keeping with the reactivities predicted on the basis of electronic and steric parameters of phenyl and methyl groups.

As a comparison, the hydrazinocarbonylation of some steroidal substrates containing the excellent triflate leaving group were also carried out. 17-Benzoyloxy-3-trifiloxy-androsta-2-ene (**6**) was reacted with phenylhydrazine and carbon monoxide under the same reaction conditions (Scheme 2). The corresponding 17-benzoyloxy-3-(*N*-(phenylamino)carbamoyl)androsta-2-ene (**6a**) was isolated in 60% yield. However, the 3-trifiloxyestra-1,3,5-(10)-trien-17-one (**7**) was totally recovered from the hydrazinocarbonylation reaction mixture. Upon addition of LiCl[13] in 3-fold excess, the target compound (3-(*N*-(phenylamino)carbamoyl)estra-1,3,5(10)-trien-17-one (**7a**)) was obtained only in traces (less than 3%), and any attempts for its isolation were unsuccessful (Scheme 2).

**Conclusion.** The high-yielding palladium-catalyzed homogeneous hydrazinocarbonylation is a powerful tool

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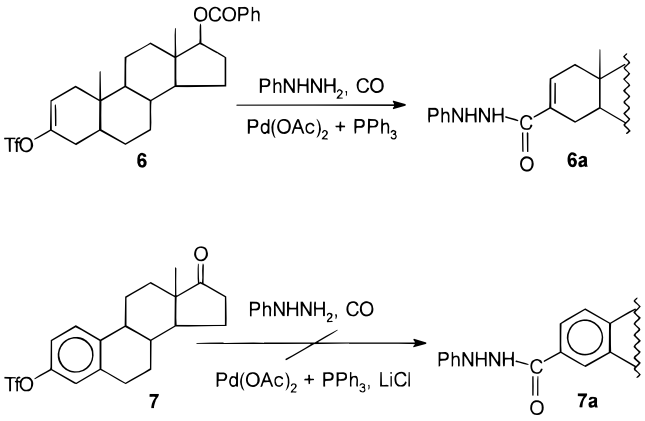
**Scheme 2. Homogeneous Catalytic Hydrazinocarbonylation of Steroidal Enol and Aryl Triflates in the Presence of Palladium Catalysts**




for the synthesis of hydrazides. Since this reaction proceeds under mild reaction conditions and tolerates various functional groups, it can widely be used for the functionalization of various skeletons of biological importance.

## Experimental Section

All experiments were carried out under carbon monoxide atmosphere. Steroidal substrates were prepared by known methods.[14] $Pd(OAc)_2$ was purchased from Ventron, and hydrazine reagents were Aldrich products.

**General Procedure for the Hydrazinocarbonylation.** A mixture of a 16-iodo(bromo)androst-16-ene derivative (1 mmol), palladium(II) acetate (11.2 mg, 0.05 mmol), triphenylphosphine (26.2 mg, 0.1 mmol), triethylamine (0.5 mL; 1 mL when 1,1-diphenylhydrazine hydrochloride was used), hydrazine (5 mmol), 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 h. Some metallic palladium was formed at the end of the reaction and was filtered off. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform and washed twice with water. The organic phase was thoroughly washed, twice with 5% HCl and then with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated to a thick red oil (when **1**, **4**, and **5** 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.

**17-(*N*-(phenylamino)carbamoyl)androst-16-ene (1a).** $^1$H NMR $\delta$: 7.35 (brs, 1H); 7.12 (m, 2H); 6.68 (m, 3H); 6.45 (m, 1H); 6.28 (m, 1H); 0.70−2.30 (m, 22H); 0.89 (s, 3H); 0.79 (s, 3H). IR (cm$^{-1}$): 1660 ($\nu$(C=O)); 1635 ($\nu$(C=O)); 1600 ($\nu$(C=C)). MS *m*/*e*: 392 (81), 285 (80), 257 (15). Anal. Calcd for $C_{26}H_{36}N_2O$ (392.58): C, 79.55; H, 9.24; N, 7.14. Found: C, 79.77; H, 9.05; N, 7.38.

**17-(*N*-(Diphenylamino)carbamoyl)androst-16-ene (1b).** $^1$H NMR $\delta$: 7.67 (brs, 1H); 7.25−6.95 (m, 10H); 6.42 (m, 1H); 0.70−2.30 (m, 22H); 0.93 (s, 3H); 0.78 (s, 3H); IR (cm$^{-1}$): 1670 ($\nu$(C=O)), 1635 ($\nu$(C=O)), 1590 ($\nu$(C=C)). MS *m*/*e*: 468 (2), 302 (10), 285 (52), 168 (100). Anal. Calcd for $C_{32}H_{40}N_2O$ (468.68): C, 82.01; H, 8.60; N, 5.98. Found: C, 82.20; H, 8.35; N, 5.79.

**17-(*N*-Amino-*N*-methylcarbamoyl)androst-16-ene (1c).** $^1$H NMR $\delta$: 5.83 (m, 1H); 4.50 (brs, 2H); 3.22 (s, 3H); 0.65−2.30 (m, 22H); 0.95 (s, 3H); 0.79 (s, 3H); IR (cm$^{-1}$): 1620 ($\nu$(C=O)), 1580 ($\nu$(C=C)). MS *m*/*e*: 330 (28), 314 (8), 285 (100), 257 (28). Anal. Calcd for $C_{21}H_{34}N_2O$ (330.51): C, 76.31; H, 10.37; N, 8.48. Found: C, 76.12; H, 10.62; N, 8.21.

**17-(*N*-(Dimethylamino)carbamoyl)androst-16-ene (1d).** $^1$H NMR $\delta$: 8.60 (brs, 1H); 6.21 (m, 1H); 2.48 (s, 6H); 0.65−2.20 (m, 22H); 0.89 (s, 3H); 0.79 (s, 3H). IR (cm$^{-1}$): 1615($\nu$(C=O)), 1575($\nu$(C=O)), 1550 ($\nu$(C=C)). MS *m*/*e*: 344 (2), 329 (2), 302 (19), 285 (35), 257 (10), 77 (100). Anal. Calcd for $C_{22}H_{36}N_2O$ (344.54): C, 76.69; H, 10.53; N, 8.13. Found: C, 76.81; H, 10.37; N, 8.38.

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**Supporting Information Available:** Analytical data ($^1$H, $^{13}$C NMR, MS, analysis) of the further steroidal hydrazides of related structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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