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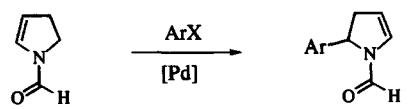
# Preparation of *N*-Formyl- and *N*-Carbomethoxy-2,3-dihydropyrroles by Palladium-Catalyzed Isomerization of the Corresponding *N*-Acyl-2,5-dihydropyrrole

Clas Sonesson[1]* and Anders Hallberg[2]

[1]Medicinal Chemistry Unit, Dept. of Pharmacology, University of Göteborg, Medicinargatan 7, S-41390 Göteborg, Sweden. [2]Dept. of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala University, P.O. Box 574, S-75123 Uppsala, Sweden.

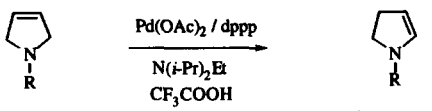
***Abstract:*** *N*-Formyl- and *N*-carbomethoxy-2,3-dihydropyrrole were prepared by palladium acetate / dppp catalyzed isomerization of *N*-formyl- and *N*-carbomethoxy-2,5-dihydropyrrole, respectively, in the presence of *N,N*-diisopropylethylamine and trifluoroacetic acid.

Cyclic enamides are versatile compounds which allow regiocontrolled functionalizations in both the α-position and the β-positions.[1] Nilsson and Hallberg have found that the reaction of enamide **1** with iodobenzene results in α-arylation and concomitant double bond isomerization, and Hayaschi *et al.* have observed that chiral induction is achieved in reactions of the corresponding *N*-carbamate with aryltriflates, employing *R*-(+)-BINAP as ligand (eq 1).[2] We preferred to prepare **1** from *N*-formylpyrrolidine by anodic methoxylation and subsequent elimination of methanol.[3] Alternative attractive methods for the synthesis of *N*-acyl-2,3-dihydropyrroles include isomerization of *N*-acyl-2,5-dihydropyrroles, utilizing $HRhCO(PPh_3)_3$ or $Fe(CO)_5$ as catalysts.[4]




**1** **2** (eq 1)

In connection with studies on the Heck arylation of *N*-acyl-2,5-dihydropyrroles, a key reaction in a preparation of C-3 arylsubstituted pyrrolidines as potential dopamine antagonists, we observed that an extensive double bond isomerization, preceeding the arylation and eventually providing analogues to **2**, occurred under certain conditions.[5] We now wish to report that *N*-formyl-2,3-dihydropyrrole **1** and *N*-carbomethoxy-2, 3-dihydropyrrole **5** are conveniently prepared by palladium-catalyzed isomerization of the corresponding *N*-formyl and *N*-carbomethoxy-2, 5-dihydropyrrolidines **3** and **4** (eq 2).




**3** R = CHO
**4** R = COOMe

**1** R = CHO (78 %)
**5** R = COOMe (80 %)

(eq 2)

Reaction of **3** or **4** (1 eq) with $Pd(OAc)_2$ (0.025 eq.) in presence of dppp (0.0275 eq.), *N,N*-diisopropylethylamine (0.30 eq.) and trifluoroacetic acid (0.15 eq) in toluene at 110° C for 24 hours under argon (g) provided isomerically pure **1** and **5** in 78% and 80% isolated yields, respectively (calculated from pure **3** and **4**).[6] Employing Pd/C as catalyst resulted in a sluggish reaction. The amine was required for catalytic activity and the use of a catalytical amount of the base (0.05 eq. sufficient for the reduction of Pd (II)[7a]) led to a very slow conversion. In the absence of trifluoroacetic acid, the reaction was accompanied by considerable aromatization of the ring system while an excess of acid was found to promote dimerization, as deduced from GC/MS. Acetate ions[7b] have been reported to promote reduction of Pd(II) by phosphine ligands,[7c] and to stabilize Pd(0).[7d]

An ethyl or methyl group at the 2-position of **4** had a deleterious effect on the isomerization rate. No conversion of the ethyl analogue occurred even after employing a long reaction time, and only a low yield (22%) of *N*-carbomethoxy-2-methyl-2,3-dihydropyrrole **6** could be isolated starting from *N*-carbomethoxy-2-methyl-2,5-dihydropyrrole (**7**).[6]

In conclusion, we believe that the palladium-catalyzed synthesis of **1** and **5** described here is a useful complement to other existing methods and merits special attention due to its ease and simplicity.

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6. Typical procedure: To a solution of **3**[8], **4**[9] or **7**[10] (3.93 mmol), *N,N*-diisopropylethylamine (160 mg,,1.24 mmol) and trifluoroacetic acid (69 mg, 0.62 mmol) in degassed toluene (4 ml) were added palladium acetate (21 mg, 94 μM) and 1,3-bis-(diphenylphosphino)-propane (dppp, 45 mg, 109 μM). The reaction mixture was stirred at 110° under an argon atmosphere for 24 h or until GC revealed no starting material. After cooling, the reaction mixture was subjected to a silica column and eluted by flash chromatography (**1**; hexane/ethyl acetate, 1:2 and **5**; hexane/diethyl ether, 1:3 and **6**; hexane/ethyl acetate, 4:1). Evaporation of the solvents afforded 297 mg of **1** (78%) or 400 mg of **5** (80%) or 122 mg of **6** (22%) with a purity > 98% (GC), as colourless liquids. Compound **1**[3]; $^1$H-NMR (300 MHz, $CDCl_3$) δ 2.7, (m, 2H), 3.8 (m, 2H), 5.25 (m, 1H), 6.45 (m, 1H), 8.4 (s, 1H). Compound **5**[1g]; δ 2.65 (m, 2H), 3.6-3.9 (m, 5H), 5.1 (br m, 1H), 6.5, 6.6 (br m, 1H). Compound **6**; δ 1.2, 1.3 (d, 3H), 2.15 (m, 1H), 2.9 (m, 1H), 3.7 (s, 3H), 4.25 (br m, 1H), 4.95 (m, 1H), 6.4, 6.6 (br m, 1H); High resolution mass spectrum calc'd for $C_7H_{11}NO_2$ ($M^+$) 141.0789; found: 141.0789
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8. Preparation of **3**: A solution of 3-pyrroline (5.0 g, Aldrich, contaminated with 25 % pyrrolidine) in ethyl formate (30 ml) was refluxed under an inert atmosphere for 12h. The solvent was removed by evaporation and the residue subjected to a silica column and eluted by flash chromathography (hexane:EtOAc, 1:2 v/v) to yield 4.5 g (a mixture of **3** and *N*-formyl-pyrrolidine: ratio 75/25): Compound **3** $^1$H NMR δ 4,2, 4.3 (m, 4H), 5.8 (m, 2H), 8.3 (s, 1H); High resolution mass spectrum calc'd for $C_5H_7NO$ ($M^+$) 97.0528, found: 97.0521.
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10. Compound **7** was prepared from **4** (0.5 g, 3.14 mmol) according to MacDonald, T.L., *J.Org.Chem.*, **1980**, *45*, 193: (1.5 eq. of methyl iodide, 2.5 eq LDA, THF). After extractive workup the residue was subjected to a silica column and eluted by flash chromathography (hexane:EtOAc, 4:1 v/v) to yield 0.13 g (30 %) $^1$H NMR δ 1.25, 1.3 (d, $J$ = 6.7 Hz, 3H), 3.7, 3.75 (s, 3H), 4.1-4.35 (m, 2H), 4.55, 4.65 (q, 1H), 5.75 (m, 2H); High resolution mass spectrum calc'd for $C_7H_{11}NO_2$ ($M^+$) 141.0789; found 141.0780


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