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Rhodium-Catalyzed Hydroformylation of 2-Vinyl- and 3-Vinyl-1-tosylpyrroles As a Convenient Synthetic Route to the Corresponding 2-(1-Tosylpyrrolyl)propanals and Derivatives

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RHODIUM-CATALYZED HYDROFORMYLATION OF 2-VINYL- AND 3-VINYL-1-TOSYLPYRROLES AS A CONVENIENT SYNTHETIC ROUTE TO THE CORRESPONDING 2-(1-TOSYLPYRROLYL)PROPANALS AND DERIVATIVES

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Abstract: 2-(1-Tosylpyrrolyl)propanals **2a-b** were conveniently prepared (70% yield) via rhodium-catalyzed hydroformylation of the corresponding 2-vinyl- and 3-vinyl-1-tosylpyrroles **1a-b** and successfully transformed into some new derivatives (50-90% yield).

In recent years the hydroformylation reaction of styrene and substituted styrenes played a very significant role in the preparation of 2-arylpropanals and derivatives of interest in the fine chemical industry[1]. On the contrary the synthetic aspect of the same process applied to the vinyl heteroaromatic substrates has been until now poorly investigated[2]. We first reported that the rhodium-catalyzed hydroformylation of the vinylpyrroles isomers can be successfully carried out to

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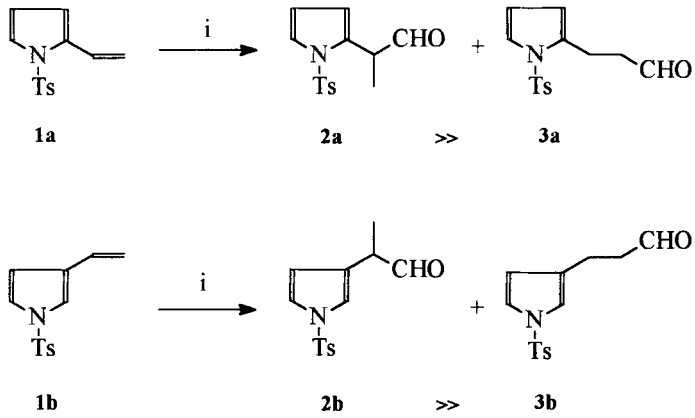
give 2-pyrrolylpropanals[3]. Whereas in the case of 1-vinylpyrrole a good yield of the corresponding branched aldehyde 2-(pyrrol-1-yl)propanal was obtained (70%), a minor amount of 2-(pyrrol-2-yl)propanal and 2-(pyrrol-3-yl)propanal was recovered from the hydroformylation of 2-vinylpyrrole and 3-vinylpyrrole respectively, side polymerization processes in these cases occurring.

Taking into account that a tosyl group on the annular nitrogen atom attenuates the normally high reactivity of the π-excessive ring and is an easily removable substituent[4], we explored the hydroformylation of the N-protected 2-vinyl-1-tosylpyrrole (**1a**)[5] and 3-vinyl-1-tosylpyrrole (**1b**)[6] respectively, under the same experimental conditions adopted for the simple vinylpyrroles[3] : the corresponding 2-(1-tosylpyrrol-2-yl)propanal (**2a**) and 2-(pyrrol-3-yl)propanal (**2b**) were obtained in very high α-regioselectivity with respect to the linear ones **3** (**2**/**3**>94/6) and good yield of isolated pure product (Scheme 1). The hydroformylation of vinylpyrroles **1a-b** was conveniently carried out in a stainless steel autoclave, at 40 °C and 120 atm total pressure (CO/H_2=1:1), in the presence of $Rh_4(CO)_{12}$ as catalyst precursor, at complete conversion of the substrate (reaction time being 24h) and substrate to catalyst ratio of 200. The solvent used was anhydrous benzene. The conversion of the substrates into aldehydes and the composition of the reaction mixtures were evaluated by GLC and GLC-MS analysis. Very high α-regioselectivity was observed, the regioisomeric ratio **2**/**3** being 94/6 in the case of **1a** and 96/4 in the case of **1b**, and similar to that detected for the corresponding N-unsubstituted vinyl substrates (94/6)[3].

Scheme 1



i: H_2/CO (1:1), 120 atm, $Rh_4(CO)_{12}$, 40 °C, benzene

Whereas the tosyl group seems to have a poor influence on the regioselectivity, the presence of this group on the annular nitrogen atom resulted very important for the reaction chemoselectivity: in both the cases the GC hydroformylation yield was very high (>92%), the hydrogenation product, deriving from H_2 addition to the exocyclic double bond, being the sole byproduct formed. No loss of the protecting group, reduction of the pyrrole nucleus or oligomers formation was detected. On this light, we tried the hydroformylation of **1a** and **1b** at higher temperature also, in order to optimize, if possible, the reaction conditions. When the hydroformylation of 3-vinyl-1-tosylpyrrole was carried out at 100°C, the branched aldehyde **2b** was still largely favoured with respect to the linear one **3b** (**2b/3b**=90/10) and a shorter reaction time was necessary (11h) to obtain complete conversion, these experimental conditions perhaps being the most convenient for the preparation of

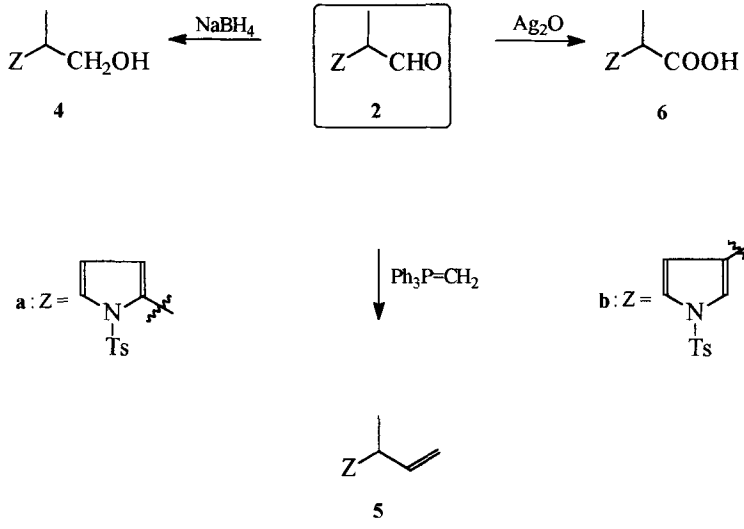
2b. A different behaviour showed 2-vinyl-1-tosypyrrole for which a consistent increase of the linear aldehyde was detected (**2a/3a**=64:36) at 100°C. In order to investigate the possible use of the reaction at high temperature as synthetic approach to **3a**, a hydroformylation run under a lower pressure[7] (30 atm) was carried out on **1a**; this way, the linear aldehyde becomes prevalent (**2a/3a**=20/80) but formation of hydrogenation product to a large extent (50%) was observed too.

The N-tosyl substitution on the pyrrole ring proved to be crucial for the isolation of the aldehydic products. Contrary to what occurred in the case of N-unprotected vinyl substrates, a good yield (70%) of isolated pure aldehydes **2a** and **2b** was obtained by liquid chromatography on a silica gel column, eluting with carbon tetrachloride-diethyl ether (80:20). These aldehydes, recovered as white solids, were characterized by ^{1}H-NMR, GC-MS and elemental analysis and were stable enough to be easily handled at room temperature. They can be stored for long periods at 0°C without any decomposition.

The easy accessibility to the N-tosylated pyrrolylpropanals suggested the use of these compounds as intermediates in the synthesis of new pyrrolyl derivatives. To this end, we submitted the N-protected pyrrolylaldehydes **2a** and **2b** to some typical reactions of the carbonyl group (Scheme 2). When **2a** and **2b** were treated with $NaBH_4$, at room temperature in anhydrous THF, the corresponding alcohols **4a-b** were obtained in high yield (87-90%). By reaction of **2a** and **2b** with triphenylmethylphosphonium bromide and butyllithium in anhydrous THF, the 3-(1-tosylpyrrolyl)but-1-enes **5a-b** were obtained (60%). The analogues of the 2-

arylpropionic acids, i.e. 2-(1-tosylpyrrolyl)propionic acids **6a** and **6b**, were prepared (50-55% yield) by treatment with Ag_2O, at room temperature. The acids were characterized as the corresponding methyl esters by reaction with ethereal diazomethane solution.

Scheme 2



The stability shown by the pyrrole ring under hydroformylation conditions and the very high α-regioselectivity of the process make the rhodium-catalyzed hydroformylation of N-tosylated vinylpyrroles **1a-b**, easily available from pyrrole in good yields, an useful and convenient synthetic method to N-tosylated-2-pyrrolylpropanals, a new class of heteroaromatic aldehydes. The accessibility of **2a** and **2b** suggests the use of these compounds as synthetic intermediates of more complex 2-pyrrolylpropanals derivatives.

Studies on the rhodium-catalyzed hydroformylation of vinylpyrroles containing various substituents on the aromatic ring as synthetic approach to polyfunctional 2-pyrrolylpropanals are now under investigation.

EXPERIMENTAL

All reagents were of commercial quality. Silica gel (70-230 mesh) was purchased from Merck.

Materials. $Rh_4(CO)_{12}$ was prepared according to a well-known procedure[8]. 2-Vinyl-1-tosylpyrrole (**1a**) was obtained by Wittig reaction on 2-formyl-1-tosylpyrrole, prepared by treatment of 2-formylpyrrole with p-toluensulfonyl chloride[5] . 3-Vinyl-1-tosylpyrrole was prepared through dehydration of the corresponding secondary carbinol deriving from the reduction of the 3-acetyl-1-tosylpyrrole prepared as reported in literature[4,6] . Melting points were taken using a Reichert Thermovar apparatus and were uncorrected .^{1}H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer with TMS as internal standard and $CDCl_3$ as the solvent. Electron impact mass spectra were recorded on a Perkin Elmer Q-Mass 910 mass spectrometer interfaced with a Perkin Elmer 8500 gas chromatograph. GC analyses of the reaction mixtures were performed on a Perkin-Elmer 8500 chromatograph equipped with a 12m x 0.22mm BP1 capillary column, using helium as carrier gas. Microanalyses were performed at Laboratorio di Microanalisi, Istituto di Chimica Organica, Facoltà di Farmacia, Università di Pisa.

General procedure for the hydroformylation of substrates ***1a-b****. 2-(1-tosylpyrrol-3-yl)propanal* ***(2b)***. A solution of **1b** (1.00 g; 4.05 mmol) and $Rh_4(CO)_{12}$ (20.2 μmol) in benzene (5 ml) was introduced in a 25 ml stainless steel reaction vessel. Carbon monoxide was introduced to the desired pressure: the autoclave was then rocked and heated to the reaction temperature and hydrogen was rapidly introduced to the desired total pressure (120 atm; CO/H_2=1/1). After 24h at 40°C the reaction was completed and regioisomeric ratio **2/3** was 96:4. From the reaction mixture 2-(1-tosylpyrrol-3-yl)propanal (**2b**) was obtained (785 mg, 4.05 mmol, 70% yield), as a white solid, by column chromatography on silica gel, by eluting with 80:20 carbon tetrachloride/ diethyl ether. Mp 69-70 °C. ^{1}H NMR δ 9.51 (d, 1H), 7.73 (d, 2H), 7.28 (d, 2H), 7.14 (m, 1H), 7.04 (m, 1H), 6.18 (m, 1H), 3.45 (q, 3H), 2.40 (s, 3H), 1.33 (d, 3H); MS m/e 277 (M+, 15), 249 (62), 221 (33), 155 (56), 91 (100), 65 (20), 32 (26). Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.21; H, 5.48; N, 5.03. *2-(1-tosylpyrrol-2-yl)propanal* ***(2a)***. 68% yield. White solid. TLC (CCl_4/Et_2O, 4/1). Mp 69 °C. ^{1}H NMR δ 9.50 (d, 1H), 7.65 (d, 2H), 7.39 (dd, 1H), 7.30 (d, 2H), 6.30 (dd, 1H), 6.13 (m, 1H), 4.15 (q, 1H), 2.40 (s, 3H), 1.28 (d, 3H); MS, m/e 277 (M+, 4), 248 (58), 155 (100), 91 (99), 65 (38), 39 (40), 29 (65). Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H 5.45; N, 5.05. Found: C, 60.45; H, 5.47; N, 5.05.

Aldehydes **2a-b** were transformed into the corresponding derivatives **4a-b**, **5a-b**, **6a-b** via standard procedures. The yields were high. All the synthesized compounds gave satisfactory analytical data, and ^{1}H NMR patterns were in

agreement with their structures.

Alcohols. Compound ***4b***. 90% yield. Pale yellow oil. TLC (Et_2O). ^1H NMR δ 7.74 (d, 2H), 7.29 (d, 2H), 7.12 (dd, 1H), 6.97 (m, 1H), 6.21 (dd, 1H), 3.57 (d, 2H), 2.82 (m, 1H), 2.41 (s, 3H), 1.63 (bs, 1H, OH), 1.18 (d, 3H); MS, m/e 279 (M+, 6), 248 (46), 155 (40), 91 (100), 65 (32). Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.21; H, 6.10; N, 5.00. *Compound* ***4a***. 87% yield. Pale yellow oil. TLC (Et_2O). ^1H NMR δ 7.62 (d, 2H), 7.29 (m, 3H), 6.25 (dd, 1H), 6.11 (dd, 1H), 3.53 (m, 3H), 2.41 (s, 3H), 1.51 (bs, 1H, OH), 1.12 (d, 3H); MS, m/e 279 (M+, 4), 248 (36), 155 (61), 91 (100), 65 (31). Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.20; H, 6.15; N, 5.01.

Olefins. Compound ***5b***. 60% yield . Pale yellow oil. TLC (CCl_4/Et_2O, 4/1). ^1H NMR δ 7.67 (d, 2H), 7.22 (d, 2H), 7.01 (dd, 1H), 6.82 (m, 1H), 6.09 (dd, 1H), 5.78 (m, 1H), 4.91 (m, 2H), 3.22 (m, 1H), 2.42 (s, 3H), 1.17 (d, 3H); MS, m/e 275 (M+, 44), 260 (32), 91 (100) , 77 (33). Anal. Calcd. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.69; H, 6.20; N, 5.11. *Compound* ***5a***. 60% yield. Pale yellow oil. TLC (CCl_4/Et_2O, 4/1). ^1H NMR δ 7.61 (d, 2H), 7.26 (m, 3H), 6.22 (t, 1H), 6.03 (m, 1H), 5.81 (m, 1H), 4.86 (m, 2H), 3.94 (m, 1H), 2.39 (s, 3H), 1.22 (d, 3H); MS, m/e 275 (M+, 11), 260 (18), 155 (28), 120 (63), 91 (100). Anal. Calcd. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.62; H, 6.20; N, 5.11.

Acids. Compound ***6b***. 55% yield . Brown oil. Anal. Calcd. for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.15; H, 5.13; N, 4.76. ^1H NMR (methyl

ester) δ 7.76 (d, 2H), 7.29 (d, 2H), 7.07 (m, 2H), 6.26 (m, 1H), 3.61 (m, 4H), 2.41 (s, 3H), 1.42 (d, 3H); MS, m/e (methyl ester) 307 (M+, 15), 248 (76), 155 (54), 91 (100), 65 (44). *Compound **6a***. Yield 50%. White solid. Mp 160-162°C. 50% yield. Anal. Calcd. for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.18; H, 5.13; N, 4.75. ^{1}H NMR (methyl ester) δ 7.67 (d, 2H), 7.28 (m, 3H), 6.25 (m, 2H), 4.18 (q, 1H), 3.56 (s, 3H), 2.41 (s, 3H), 1.44 (d, 3H); MS, m/e (methyl ester) 307 (M+, 32), 248 (100), 155 (40), 91 (63), 65 (16).

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