Synthesis of 5,6,7,8-Tetrahydroindolizines *via* a Domino-Type Transformation Based on the Rhodium Catalyzed Hydroformylation of *N*-(β-Methallyl)pyrroles

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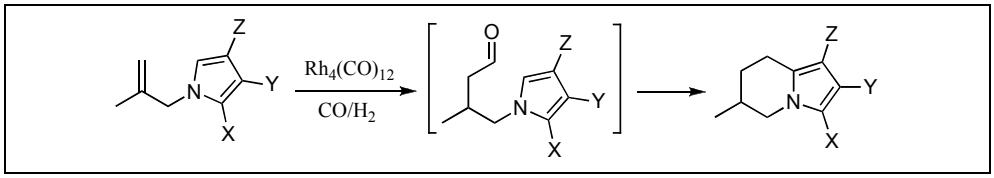

Variously substituted 5,6,7,8-tetrahydroindolizines can be easily synthesized *via* a domino reactions sequence under rhodium catalyzed hydroformylation of *N*-(β-methallyl)pyrroles. The later are readily prepared from properly functionalized pyrroles *via* phase-transfer N-allylation in the presence of 18-crown-6 and potassium *tert*-butoxide.

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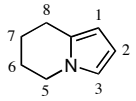
INTRODUCTION



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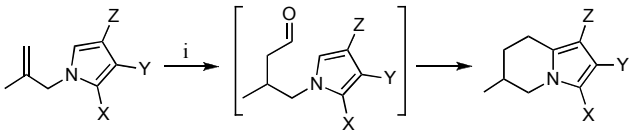
The tetrahydroindolizine framework **1** and its oxidized and reduced forms are frequently found in a wide array of alkaloids and other pharmaceutically important natural and synthetic compounds. The base-structure **1** is present in (-)-rhazinilam, an alkaloid isolated from different Apocynaceae species, and inhibits disassembly of microtubole [1].

Variously substituted 5,6,7,8-tetrahydroindolizines are dopaminergic ligands [2], anti-TNF agents [3], as well as useful intermediates in the synthesis of the corresponding fully unsaturated indolizines or hydrogenated indolizidines [4]. Although 5,6,7,8-tetrahydroindolizine has been obtained many years ago by catalyzed hydrogenation of indolizine [5], the isolation from natural sources, synthesis, and the study of the biological properties of analogous molecules is still a research field of great interest and continuous evolution.

Among the synthetic approaches starting from pyrrole derivatives, radical or cationic cycloadditions [6a,2] and intramolecular cyclizations based on benzotriazole-methodology have been recently reported [6b]. With respect to multi-steps reactions, domino-type sequences are very powerful synthetic tools because they rapidly increase the complexity of a substrate while at the same time make economical use of available functional groups [6c]. In the frame of our studies on the rhodium catalyzed hydroformylation of olefins as synthetic instrument for fine chemistry [7-8], we found a general domino protocol to 5,6,7,8-tetrahydroindolizines. It is based on the rhodium catalyzed hydroformylation of the differently substituted *N*-(β-methallyl)pyrroles (**2**): under these conditions the formed 4-(pyrrol-1-yl)butanals (**3**) undergo an *in situ* intramolecular cyclization followed by hydrogenation of the six membered ring to selectively give the 6-methyltetrahydroindolizines (**4**) (Scheme 1).

Scheme 1



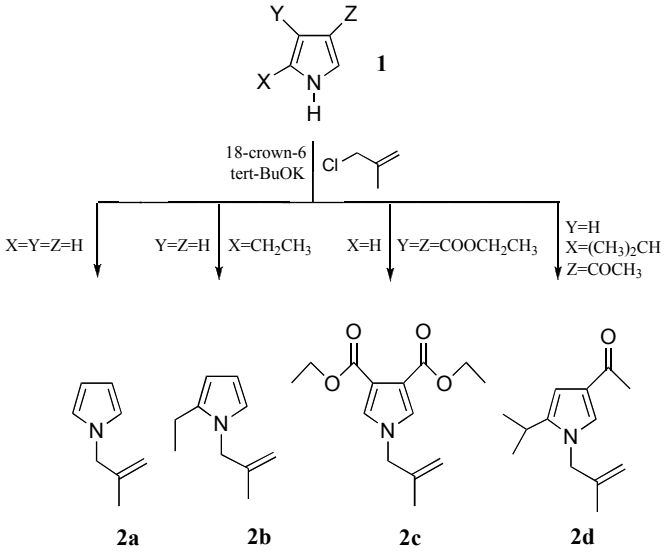
2 **3** **4**

i: $Rh_4(CO)_{12}$, 130 atm, CO/H_2=1/1, 140°C, toluene, 10- 72 h

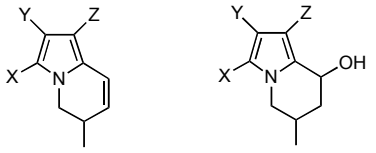
RESULTS AND DISCUSSION

The differently substituted N-allylpyrroles (**2a-d**) were prepared *via* N-allylation of the proper pyrroles (**1a-d**) (Scheme 2). This step was accomplished in diethyl ether *via* a phase-transfer process in which 18-crown-6 was employed as the catalyst and potassium *tert*-butoxide was employed as the base [9]. In this way **2a** was obtained in a higher yield with respect to the previous one reported [7c]. In the case of the preparation of **2a-c** the proper pyrroles were commercially available. In contrast in the case of the preparation of **2d**, 2-*i*-propyl-3-acetylpyrrole was obtained from 3-acetylpyrrole [10a] *via* alkylation on the 2-pyrrole position with isopropyl chloride at 50 °C, according to a method reported in literature [10b].

Scheme 2



With respect to a typical hydroformylation experiment [7c,11] stressed temperature and pressure values were applied together with longer reaction times. The substrates **2a-d** were inserted into a 25 ml stainless autoclave in the presence of $Rh_4(CO)_{12}$ as the catalyst precursor, at 140 °C, under a pressure of 130 atm ($CO:H_2$ 1:1), in toluene as a solvent. Under the above conditions the sole formed aldehydes **3** (Scheme 1) evolve to the indolizine skeleton *via* an *in situ* intramolecular cyclization on the α-pyrrole position by the carbonyl carbon atom followed by reduction of the six membered ring. Very different reaction times were necessary in dependence on the substituents nature. For **2c**, bearing two electron-withdrawing groups on the pyrrole ring, 72 h were necessary in order to observe a complete conversion into **4c**. On the contrary **2b**, characterized by the presence of the electron-donating ethyl group on the 2-pyrrole position, was converted into **4b** within 10 hours. Intermediate values of reaction time were observed for **2a** and **2d**. The cyclization step conditions the global process rate. It is greater when no groups or an electron-donating group are present on the pyrrole ring (case of **2a-b**): thus no traces of the pyrrolylbutanals **3a-b** were observed at all conversions but directly the corresponding 5,6-dihydroindolizine intermediates **IIa-b** (GC-MS control) [12] deriving from an intramolecular cyclodehydration [7a] of **3a-b**. The successive hydrogenation of the double bond in the six membered ring gave rise to the structures **4a-b**. In the case of **2c** and **2d**, the evolution of the corresponding aldehydes **3c** and **3d** to **4c** and **4d** respectively is slower and *via* two possible intermediates: the 5,6-dihydroindolizines **IIc-d**, as for **2a** and **2b**, or the bicyclic alcohols **IIIc-d** as evidenced in the case of the hydroformylation of 3-acetyl-1-β-methallylpyrrole [13]. Thus **4** could form from **II** *via* a double bond hydrogenation or from **III** *via* a direct hydrogenolysis of the hydroxyl group.



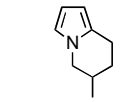
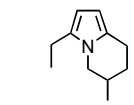
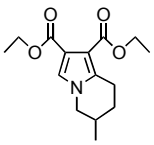
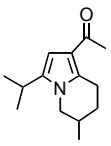
a X=Y=Z=H **c** X=H Y=Z= $COOCH_2CH_3$
b X=Et, Y=Z=H **d** X=*i*-Pr, Y= H, Z=$COCH_3$

An intermediate of the **III** type has been evidenced in the case of **2d** [14]: this structure could be favoured by an intramolecular hydrogen bond between the hydrogen of the hydroxyl group and the carbonyl substituent on the β-pyrrole position.

All synthesized tetrahydroindolizines **4** are new compounds: they have been isolated and characterized and can be stored at 0 °C for long periods of time without decomposition.

To sum up, starting from *N*-β-methallylpyrroles the corresponding 6-methyl-5,6,7,8-tetrahydroindolizines have been obtained under rhodium-catalyzed hydroformylation conditions in a one-pot domino operation. Electron-withdrawing or electron-donating substituents on both pyrrole ring or alkyl chain do not affect the sequence selectivity and the good yield of the final products. All transformations employ inexpensive reagents and provide pure products after a simple purification process. It is worth noting that indolizines with various degrees of unsaturation are common in nature and they are characterized by different physiological activities [2,3]. On this light we think that the domino-type transformation described by us represents a convenient addition to the pyrrole chemistry.

Table 1

Entry	**4**	Yield %	Purification process
a		63	Colorless oil Al_2O_3; hexane
b		60	Colorless oil Al_2O_3; hexane
c		75	Yellow oil Al_2O_3; hexane/acetone (70/30)
d		70	Yellow oil Al_2O_3, benzene/AcOEt (80/20)

EXPERIMENTAL

All reagents were of commercial quality. TLC analyses were performed on aluminum oxide 60 F_{254} neutral plates from Merck. For preparative chromatography Merck aluminum oxide 90 active (neutral, 70-230 mesh) was used. Toluene was dried over molecular sieves and distilled under nitrogen. ^{1}H NMR spectra were recorded on a Varian Gemini 200 at 200 MHz for ^{1}H and 50 MHz for ^{13}C with TMS as internal standard and $CDCl_3$ as the solvent. GC analyses were performed on a Perkin Elmer 8700 chromatograph equipped with a 15 m x 0.25 mm BP1 capillary column, using nitrogen as carrier gas. GC/MS analyses were performed on a Perkin Elmer Q-Mass 910 interfaced with a Perkin Elmer 8500 chromatograph equipped with a 30 m x 0.25 mm apolar 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. $Rh_4(CO)_{12}$ was prepared according to a known procedure [15].

Typical Procedure for the Preparation of the Pyrroles 2. To a solution of 18-crown-6 (0.25 mmoles) in 20 ml of anhydrous Et_2O was added potassium *tert*-butoxide (2.8 mmoles). The mixture was stirred magnetically while the pyrrole derivative **1** (2.4 mmoles) was introduced in a single portion. Stirring was continued for 15 min and then 3-chloro-2-methyl-1-propene (2.8 moles) dissolved in 10 ml of anhydrous Et_2O was added dropwise to the reaction mixture cooled in an ice bath. The mixture was then allowed to warm up to room temperature and, after complete conversion of the reagent was achieved (GC), water was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic solution was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give **2** as crude products.

2-Methyl-3-(pyrrol-1-yl)prop-1-ene (2a). 75 % yield. Colorless liquid; bp 32 °C, 1.5 mmHg. ^{1}H nmr δ 6.67 (t, J=2.1 Hz, 2H, Pyr), 6.19 (t, J=2.1 Hz, 2H, Pyr), 4.92 (s, 1H, CH_2=), 4.77 (s, 1H, CH_2=), 4.43 (s, 2H, CH_2-N), 1.68 (s, 3H, CH_3). ^{13}C nmr δ 19.8, 55.9, 108.2 (2 $C_{\beta pyr}$), 112.8, 121.2 (2$C_{\alpha pyr}$), 142.3. MS m/z 121 (M^+, 68), 120 (65), 106 (100), 80 (99), 53 (16). *Anal.* Calcd for $C_8H_{11}N$: C, 79.34; H, 9.10; N, 11.57. Found: C, 79.45; H, 9.12; N, 11.59.

2-Methyl-3-(2-ethylpyrrol-1-yl)prop-1-ene (2b). 70 % yield, as a yellow oil. ^{1}H nmr δ 6.55 (t, J=1.6 Hz, 1H, Pyr), 6.09 (t, J=3.1 Hz, 1H, Pyr), 5.92 (m, 1H, Pyr), 4.83 (m, 1H, CH_2=), 4.48 (s, 1H, CH_2=), 4.30 (s, 2H, CH_2-N), 2.50 (q, J=7.4 Hz, 2H, C*H*$_2$-CH_3), 1.69 (s, 3H, CH_3), 1.24 (t, J=7.4 Hz, 3H, CH_2-C*H*$_3$). ^{13}C nmr δ 13.0, 19.4, 20.0, 52.6, 104.8, 106.8, 111.7, 120.8, 135.2, 142.3. MS m/z 149 (M^+, 60), 134 (100), 120 (39), 93 (18), 80 (27), 55 (41). *Anal.* Calcd for $C_{10}H_{15}N$: C, 80.54; H, 10.07; N, 9.40. Found: C, 80.70; H, 10.08; N, 9.42.

Diethyl 1-(2-methylprop-2-enyl)-3,4-pyrroledicarboxylate (2c). 75% yield, as a yellowish oil. ^{1}H nmr δ 1.39 (t, J=7.1 Hz, 6H, CH_3), 1.73 (s, 3H, CH_3), 4.36 (q, J=7.1 Hz, 4H, C*H*$_2$-CH_3), 4.42 (s, 2H, CH_2-N), 4.91 (s, 1H, CH_2=), 5.05 (s, 1H, CH_2=), 7.27 (s, 2H, Pyr). ^{13}C nmr δ 14.5 (2 CH_3), 19.8, 56.7, 60.4 (2 CH_2-O), 115.0, 116.5 (2 $C_{\beta\ pyr}$), 128.2 (2 $C_{\alpha\ pyr}$), 140.2, 163.9 (2 CO). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.40; H, 7.17; N, 5.28. Found: C, 63.32; H, 7.15; N, 5.26.

1-[5-*i*Propyl-1-(2-methylallyl)pyrrol-3-yl]ethanone (2d). 78 % yield, as a yellowish oil. ^{1}H nmr δ 1.21 (d, J=7.1 Hz, 6H, CH_3), 1.71 (s, 3H, CH_3), 2.36 (s, 3H, CH_3CO), 2.75 (sept, J=7.1 Hz, 1H, CH), 4.35 (s, 2H, CH_2-N), 4.53 (s, 1H, CH_2=), 4.91 (s, 1H, CH_2=), 6.37 (d, J=1.8 Hz, 1H, Pyr), 7.15 (d, J=1.8 Hz, 1H, Pyr). ^{13}C nmr δ 20.1, 23.3 (2 CH_3 of *i*-Pr), 25.5, 38.7, 53.0, 103.2, 104.1, 112.9, 126.5, 132.2, 141.4, 192.7. MS m/z 205 (M^+, 31), 190 (100), 162 (19), 148 (38), 120 (25), 77 (18), 55 (71). *Anal.* Calcd for $C_{13}H_{19}NO$: C, 78.79; H, 8.22; N, 6.06. Found: C, 78.86; H, 8.21; N, 6.05.

Typical Procedure for the Preparation of 5,6,7,8-Tetrahydroindolizines 4. A solution of **2** (0.8 mmole) and $Rh_4(CO)_{12}$ (5 mg, $7x10^{-3}$ mmole, substrate/Rh= 115/1) in toluene (5 ml) was introduced by suction into an evacuated 25 ml stainless steel reaction vessel. Carbon monoxide was introduced, the autoclave was then rocked, heated to 140 °C and hydrogen was rapidly introduced to 130 atm (CO/H_2=1:1) total pressure. The degree of conversion and the product distributions were determined by GC/GC-MS (in the case of **2a-b** and **2d**) with use of n-decane as internal standard or ^{1}H NMR (case of **2c**). Then the reaction mixture was siphoned out, the solvent was evaporated under reduced pressure and the residue was eluted on chromatographic column (Table 1).

6-Methyl-5,6,7,8-tetrahydroindolizine (4a). Colorless oil. ^{1}H nmr δ 1.13 (d, J=6.6 Hz, 3H, CH_3), 1.50 (m1H, C*H*$_2$-CH), 1.98 (m, 1H, C*H*$_2$-CH), 2.12 (m, 1H, CH), 2.70-3.02 (m, 2H, CH_2-C=, CH_2-N), 3.45 (t, J=11.5 Hz, 1H, CH_2-C=), 4.05 (dd, J=5.5; 11.1 Hz, 1H, CH_2-N), 5.90 (bs, 1H, Pyr), 6.19 (m, 1H, Pyr), 6.55 (m, 1H, Pyr). ^{13}C nmr δ 19.4, 23.2, 30.2, 30.4, 52.5, 103.9, 107.9, 118.6, 129.0. MS m/z 135 (M^+, 92), 134 (100), 120 (32), 106 (18), 93 (71), 80 (25). *Anal.* Calcd for $C_9H_{13}N$: C, 80.00; H, 9.63; N, 10.37. Found: C, 80.24; H, 9.65; N, 10.38.

3-Ethyl-6-methyl-5,6,7,8-tetrahydroindolizidine (4b). Colorless oil. ^{1}H nmr δ 1.18 (d, J=6.6 Hz, 3H, CH_3), 1.33 (t, J=7.5 Hz, 3H, C*H*$_3$-CH_2), 1.50 (m, 1H, C*H*$_2$-CH), 1.92-2.24 (m, 2H, C*H*$_2$-CH, CH), 2.56 (q, 2H, J=7.5 Hz, C*H*$_2$-CH_3), 2.75-3.03 (m, 2H, CH_2-C=, CH_2-N), 3.27 (t, J=11.1 Hz, 1H, CH_2-C=), 3.97 (dd, J= 5.1; 14.0 Hz; 1H, CH_2-N), 5.93 (bs, 2H, Pyr). ^{13}C nmr δ 12.9, 19.5, 19.5, 23.4, 29.8, 29.9, 49.7, 102.8, 103.7, 128.1, 132.9. MS m/z 163 (M^+, 34), 148 (100), 134 (7), 106 (12), 93 (7). *Anal.* Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 81.30; H, 10.40; N, 8.60.

Diethyl6-methyl-1,2-(5,6,7,8-tetrahydroindolizine)dicarboxylate (4c). Colorless oil. ^{1}H nmr δ 1.07 (d, J=6.6 Hz, 3H, CH_3), 1.31 (t, J=6.6 Hz, 6H, CH_3), 1.40 (m, 1H, C*H*$_2$-CH), 1.94-2.04 (m, 2H, C*H*$_2$-CH, CH), 2.81 (m, 1H, CH_2-C=). 3.21 (m, 1H, CH_2-N), 3.42 (t, J=11.2 Hz, 1H, CH_2-C=), 3.95 (dd, J=5.4; 12.6 Hz, CH_2-N), 4.27 (q, J=6.6 Hz, 4H, C*H*$_2$-CH_3), 6.99 (s, 1H, Pyr). ^{13}C nmr δ 14.7 (2 CH_3), 18.9, 23.1, 29.1, 30.0, 52.8, 60.4 (2 CH_2-O), 107.4, 108.2, 124.9, 136.0, 164.9 (2 CO). *Anal.* Calcd for $C_{15}H_{21}N$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.48; H, 7.52; N, 5.00.

1-(3-*i*Propyl-6-methyl-5,6,7,8-tetrahydroindolizin-1-yl)ethanone (4d). Colorless oil. ^{1}H nmr δ 1.18 (d, J=6.6 Hz, 3H, CH_3), 1.33 (d, J=6.8 Hz, 6H, CH_3), 1.47 (m, 1H, C*H*$_2$-CH), 1.90-2.19 (m, 2H, CH, C*H*$_2$-CH), 2.45 (s, 3H, CH_3CO), 2.86-3.05 (m, 2H, C*H*$(CH_3)_3$, CH_2-C=), 3.35-3.54 (m, 2H, CH_2-C=, CH_2-N), 4.04 (dd, J=4.3; 11.9 Hz, 1H, CH_2-N), 6.32 (s, 1H, Pyr). ^{13}C nmr δ 19.3, 22.9 (2 CH_3), 23.0, 24.5, 25.4, 28.6, 29.1, 49.9, 104.8, 105.4, 138.5, 138.9, 196.5. MS m/z 219 (M^+, 25), 205 (33), 204 (100), 176 (11). *Anal.* Calcd for $C_{14}H_{21}N$: C, 76.71; H, 9.59; N, 6.39. Found: C, 76.55; H, 9.58; N, 6.41.

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[12] Typical GC-MS data for **IIa**: MS m/z 133 (M^+, 45), 132 (23), 118 (100), 117 (50), 91 (20). Typical GC-MS data for **IIb**: MS m/z 161 (M^+, 48), 146 (100), 144 (9).

[13] R. Settambolo, S. Rocchiccioli, R. Lazzaroni and G. Alagona, *Lett. in Org. Chem*., **3**, 10 (2006).

[14] Typical GC-MS data of **IIId**: Ms m/e 235 (M^+, 39), 220 (48), 217 (43), 202 (100), 192 (45), 160 (20), 144 (24), 77 (15). The precursor **3d** shows the same significant fragments. In the case of **2c** the GC-MS analysis was unsuccessful and the conversion into **4c** was monitored *via* TLC on Al_2O_3 by eluting with hexane/acetone (70:30).

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