Pergamon

Tetrahedron Letters 42 (2001) 4045–4048

TETRAHEDRON LETTERS

An original approach to 5,6-dihydroindolizines from 1-allylpyrroles by a tandem hydroformylation/cyclization/dehydration sequence

Roberta Settambolo,[a] Aldo Caiazzo[b] and Raffaello Lazzaroni[b,*]

[a]*Istituto di Chimica Quantistica ed Energetica Molecolare del CNR, Via Alfieri 1, 56010 Ghezzano (PI), Italy*
[b]*Dipartimento di Chimica e Chimica Industriale, Via Risorgimento 35, 56126 Pisa, Italy*

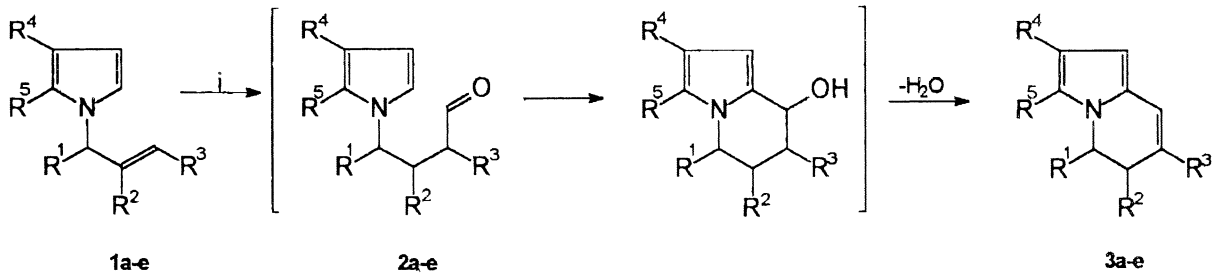
Received 2 February 2001; accepted 11 April 2001

Abstract—6-Methyl-5,6-dihydroindolizine and 3- or 2-ethyl derivatives were obtained via a one-pot hydroformylation/cyclization/dehydration sequence starting from 1-(2-methyl-2-propenyl)pyrroles. 7-Phenyl-5,6-dihydroindolizine and 5-methyl-5,6-dihydroindolizine were similarly synthesized. An easily occurring electrophilic aromatic substitution by the carbon atom of the carbonyl group on the α-position of the pyrrole ring with the formation of the six-membered ring is the key-step of the process.

The hydroformylation of functionalized unsaturated substrates, especially when involved in tandem or domino reaction sequences, constitutes a very versatile tool for the synthesis of fine chemicals.[1] Thus, reduction, nucleophilic addition or aldol condensation can be achieved directly under the reaction conditions of the oxo process.[1]

During our studies on the factors affecting the regioselectivity of the rhodium-catalyzed hydroformylation of vinyl[2] and allyl[3] heteroaromatic substrates, we found that 4-(pyrrol-1-yl)butanal, obtained as the minor product (20%) in the 1-allylpyrrole hydroformylation, surprisingly gave 5,6-dihydroindolizine via a one-pot cyclization/dehydration process.[3]

5,6-Dihydro- and 5,6,7,8-tetrahydroindolizines are some of the most intriguing fused pyrrole derivatives, because they constitute the basic skeleton of many natural alkaloids and possess pharmacological proper-



1a-e **2a-e** **3a-e**

i: CO/H_2 100 atm (1:1), $Rh_4(CO)_{12}$, toluene, 100°C

a: $R^1=R^3=R^4=R^5=H$ $R^2=Me$
b: $R^1=R^2=R^4=R^5=H$ $R^3=Ph$
c: $R^1=R^3=R^4=H$ $R^2=Me$ $R^5=Et$
d: $R^1=R^3=R^5=H$ $R^2=Me$ $R^4=Et$
e: $R^1=Me$ $R^2=R^3=R^4=R^5=H$

Scheme 1.

Keywords: hydroformylation; indolizine; rhodium; catalyst.
* Corresponding author. Tel.: (050) 918227; fax: (050) 918260; e-mail: lazza@dcci.unipi.it

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00625-6

ties.[4] Thus, the design of new synthetic methods for this class of compound is an interesting and topical subject. The unexpected result obtained in the hydroformylation of 1-allylpyrrole prompted us to investigate the synthetic potentiality of this method by submitting to hydroformylation suitable 1-allylpyrroles which are able to generate 4-(pyrrol-1-yl)butanals or, more generally, 4-(pyrrol-1-yl)alkanals, possible precursors of 5,6-dihydroindolizines. We found and report here that when the easily available 1-(2-methyl-2-propenyl)pyrrole (**1a**) and 1-(3-phenyl-2-propenyl)pyrrole (**1b**) are submitted to rhodium-catalyzed hydroformylation, 5,6-dihydroindolizines **3a**–**b** substituted on the six-membered ring are obtained as the exclusive products (Scheme 1).

Under the same experimental conditions, 2-ethyl-1-(2-methyl-2-propenyl)pyrrole (**1c**) and 3-ethyl-1-(2-methyl-2-propenyl)pyrrole (**1d**) selectively give 5,6-dihydroindolizines **3c**–**d**, substituted on both the rings of the indolizine moiety (Scheme 1), while the vinyl substrate 1-(1-methyl-2-propenyl)pyrrole (**1e**) gives 5-methyl-5,6-dihydroindolizine (**3e**) (Scheme 1).

1-Allylpyrroles[5] **1a**–**e** were easily prepared from the reaction between the corresponding pyrrole compound and the appropriate allyl halide in the KOH/DMSO system.[3,6] The hydroformylation of the substrates **1a**–**e** was carried out in the presence of $Rh_4(CO)_{12}$ as catalyst precursor[7,8] according to a typical procedure.[9]

By using a Rh/substrate ratio of 1:100, the olefin **1a** was totally converted into 6-methyl-5,6-dihydroindolizine (**3a**) in a short time (0.5 h) (Scheme 1). In order to slow down the reaction, a Rh/substrate ratio of 1:1000 was employed: at 10% conversion, a small amount of aldehyde **2a** was detected in the reaction mixture,[10] the indolizine formation still being a fast process with respect to the oxo one. On the other hand, attempts to carry out the reaction at lower temperatures were unsuccessful, **1a** remaining unreacted.

When **1b** was submitted to rhodium-catalyzed hydroformylation under the same conditions as for **1a**, 7-phenyl-5,6-dihydroindolizine **3b** was obtained as the exclusive product (Scheme 1). In this case no traces of 2-phenyl-4-(pyrrol-1-yl)butanal (**2b**), the precursor to **3b**, were observed even at very low conversions, the cyclization/dehydration being very fast with respect to the hydroformylation reaction. It is worth noting that in both cases the hydroformylation occurs with complete regioselectivity. In the presence of **1a**, the exclusive addition of the formyl group to the terminal carbon atom takes place according to behavior typical of disubstituted terminal olefins.[11] In the case of **1b**, exclusive addition of the formyl group to the carbon atom directly bonded to the phenyl group occurs, the pyrrolyl olefin **1b** showing behavior typical of styrene.[12]

In order to explore the possibility of obtaining dihydroindolizines selectively functionalized on the pyrrole ring, we submitted to hydroformylation 2- or 3-ethyl-1-(2-methyl-2-propenyl)pyrroles **1c**–**d** (Scheme 1): with these substrates 5,6-dihydroindolizines **3c**–**d** were also obtained with very high chemo- and regioselectivity (Scheme 1). In the case of **1c**, 3-ethyl-6-methyl-5,6-dihydroindolizine (**3c**) was formed as the sole reaction product. In the case of **1d**, both the 2 and 5 positions of the pyrrole ring were involved in the cyclization process, but the 2-ethyl-6-methyl-5,6-dihydroindolizine **3d**, coming from annulation on the pyrrole C5 carbon atom, was largely prevalent with respect to the 1-ethyl-6-methyl-5,6-dihydroindolizine **3′d**, which had involved the pyrrole C2 carbon atom (**3d**/**3′d** = 90:10). It is worth noting that no traces of the expected oxo pyrrolylbutanals, precursors to the dihydroindolizines **3c**–**d**, were found in the crude reaction mixtures at any degree of conversion: these aldehydes, as they form, immediately react with the cyclization process.

The hydroformylation of the vinyl substrate 1-(1-methyl-2-propenyl)pyrrole (**1e**) under the same experimental conditions gives, in addition to 2-methyl-3-(pyrrol-1-yl)butanal (**2′e**),[13] 5-methyl-5,6-dihydroindolizine (**3e**) in a **3e**/**2′e** = 59/41 molar ratio. The linear aldehyde **2e**, the precursor to **3e**, was present only in traces in the reaction mixture both at partial and complete substrate conversion. On carrying out the hydroformylation of **1e** at a higher temperature (120°C) and lower pressure (30 atm $CO/H_2 = 1:1$), the molar ratio **3e**/**2′e** conveniently increased to 78/22, according to the well documented behavior of vinyl and allyl substrates.[3,12] Interestingly 5-methyl-5,6-dihydroindolizine (**3e**) is a suitable precursor to 5-methyloctahydroindolizine, the simplest 5-alkylsubstituted indolizidine,[14] which are a well-known family of natural indolizidine alkaloids.[15] The dihydroindolizines **3a**–**e** are new compounds and were isolated and characterized by ^1H and ^{13}C NMR spectroscopy, GC–MS, melting point and elemental analysis.[16] They are stable enough to be handled easily at room temperature without any decomposition and can be stored at 0°C for long periods.

In conclusion, the chemistry reported here is an interesting application of the rhodium-catalyzed hydroformylation providing a concise synthesis of alkyl substituted 5,6-dihydroindolizines starting from easily available allylpyrroles via a one-pot 4-(pyrrol-1-yl)butanal formation and intramolecular cyclization. The key-step of the sequence consists of an intramolecular electrophilic aromatic substitution promoted by the carbon atom of the carbonyl group on the C2 (5) carbon atom of the pyrrole ring. The reaction occurs under mild conditions even in the absence of classical Lewis acids, likely due to the strong nucleophilic character of the pyrrole carbon atom α to the nitrogen. It is worth remarking that, while the intramolecular cyclization of 4-(pyrrol-1-yl)alkanoic acids or alkanoates is a well-known process catalyzed by Lewis acid,[4b,14] the construction of the indolizine skeleton via annulation of 4-(pyrrol-1-yl)butanals has been reported here for the first time.

Acknowledgements

This work was partially supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (40% funds).

References

1. Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329.
2. (a) Caiazzo, A.; Settambolo, R.; Pontorno, L.; Lazzaroni, R. *J. Organomet. Chem.* **2000**, *599*, 298; (b) Settambolo, R.; Caiazzo, A.; Lazzaroni, R. *J. Organomet. Chem.* **1996**, *506*, 337.
3. Lazzaroni, R.; Settambolo, R.; Caiazzo, A.; Pontorno, L. *J. Organomet. Chem.* **2000**, *601*, 320.
4. (a) Katritzky, A. R.; Fali, C. N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4148 and references cited therein; (b) Sayah, B.; Pelloux-Léon, N.; Vallée, Y. *J. Org. Chem.* **2000**, *65*, 2824.
5. **1a** (63% yield), colorless liquid. Bp 31°C, P 1.5 mmHg. ^{1}H NMR δ 6.67 (t, J=2.1 Hz, 2H), 6.19 (t, J=2.1 Hz, 2H), 4.92 (s, 1H), 4.77 (s, 1H), 4.43 (s, 2H), 1.68 (s, 3H). MS m/e 121 (M^+, 68), 120 (65), 106 (100), 80 (99), 53 (16). **1b** (40% yield), yellow oil. ^{1}H NMR δ 7.50–7.20 (m, 5H), 6.71 (t, J=2.1 Hz, 2H), 6.49 (d, J=15.8 Hz, 1H), 6.30 (m, 1H), 6.16 (t, J=2.1 Hz, 2H), 4.64 (d, J=5.9 Hz, 2H). MS m/e 183 (M^+, 52), 118 (10), 117 (100), 115 (76). **1c** (68% yield), yellow oil. ^{1}H NMR δ 6.55 (t, J=1.6 Hz, 1H), 6.09 (t, J=3.1 Hz, 1H), 5.92 (m, 1H), 4.83 (m, 1H), 4.48 (s, 1H), 4.30 (s, 2H), 2.50 (q, J=7.4 Hz, 2H), 1.69 (s, 3H), 1.24 (t, J=7.4 Hz, 3H). MS m/e 149 (M^+, 60), 134 (100), 120 (39), 93 (18), 80 (27), 55 (41). **1d** (65% yield), yellow oil. ^{1}H NMR δ 6.55 (m, 1H), 6.40 (s, 1H), 6.00 (m, 1H), 4.85 (s, 1H), 4.75 (s, 1H), 4.30 (s, 2H), 2.45 (q, J=5.0 Hz, 2H), 1.65 (s, 3H), 1.20 (t, J=5.0 Hz, 3H). MS m/e 149 (M^+, 65), 134 (100), 120 (37), 93 (18), 80 (24), 55 (38). **1e** (68% yield), colorless liquid. ^{1}H NMR δ 6.72 (t, J=2.1 Hz, 2H), 6.16 (t, J=2.1 Hz, 2H), 5.98 (m, 1H), 5.02–5.20 (m, 2H), 4.65 (m, 1H), 1.55 (d, J=7.0 Hz, 3H). MS m/e 121 (M^+, 74), 106 (95), 79 (27), 67 (100), 55 (54).
6. (a) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 49; (b) Patterson, J. M.; De Haan, J. W.; Boyd, M. R.; Ferry, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 2487.
7. McCleverty, J. A.; Wilkinson, G. *Inorg. Synth.* **1966**, *8*, 211.
8. Cattermole, P. E.; Osborne, G. A. *Inorg. Synth.* **1977**, *17*, 115.
9. *Hydroformylation of 1-allylpyrroles **1a–e**. General procedure. Preparation of 6-methyl-5,6-dihydroindolizine (**3a**).* A solution of 1-(2-methyl-2-propenyl)pyrrole (**1a**) (0.5 g, 4.13 mmol) and $Rh_4(CO)_{12}$ (7.5 mg, substrate/Rh = 100/1) in toluene (10 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 100°C and hydrogen was rapidly introduced to 100 atm (CO/H_2=1/1) total pressure. After 0.5 h at 100°C the reaction was completed and formation of a single product was observed. From the reaction mixture 6-methyl-5,6-dihydroindolizine (**3a**) was obtained as a red oil (SiO_2; hexane/EtOAc=4:1) (0.41 g, 75% yield); ^{1}H NMR δ 6.56 (bs, 1H), 6.37 (dd, J=9.9; 2.1 Hz, 1H), 6.11 (t, J=3.0 Hz, 1H), 6.02 (m, 1H), 5.55 (dd, J=9.9; 3.6 Hz, 1H), 3.95 (dd, J=12.0; 6.0 Hz, 1H), 3.51 (dd, J=12.0; 9.6 Hz, 1H), 2.75 (m, 1H), 1.15 (d, J=6.9 Hz, 3H); ^{13}C NMR δ 128.1, 126.0, 121.0, 119.0, 108.0, 105.5, 51.0, 29.8, 18.2. MS m/e 133 (M^+, 45), 132 (23), 118 (100), 117 (50), 91 (20). Anal. calcd for $C_9H_{11}N$: C, 81.20; H, 8.27; N, 10.53. Found: C, 81.35; H, 8.22; N, 10.55.
10. Aldehyde **2a** was characterized in the crude reaction mixture with **3a**. **2a**: ^{1}H NMR δ 9.61 (t, J=1.5 Hz, 1H, CHO), 6.55 (s, 2H, Pyr), 6.14 (s, 2H, Pyr), 3.85–3.69 (m, 2H, N-CH_2), 2.51 (m, 1H, CH), 2.38–2.20 (m, 2H, CHO-C$\underline{H}_2$), 0.97 (d, J=7.1 Hz, 3H, CH_3). MS m/e 151 (M^+, 24), 123 (60), 81 (92), 80 (100).
11. (a) Matsui, Y.; Orchin, M. *J. Organomet. Chem.* **1983**, *57*, 246; (b) Lazzaroni, R.; Settambolo, R.; Uccello-Barretta, G.; Caiazzo, A.; Scamuzzi, S. *J. Mol. Catal. A: Chem.* **1999**, *143*, 123.
12. Lazzaroni, R.; Raffaelli, A.; Settambolo, R.; Bertozzi, S.; Vitulli, G. *J. Mol. Catal.* **1989**, *50*, 1.
13. As shown by GC and GC–MS analyses of the reaction mixtures, **2′e** was formed as a pair of diastereomers (diastereomeric ratio was 60/40).
14. Bond, T. J.; Jenkins, R.; Ridley, A. C.; Taylor, P. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2241.
15. (a) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103; (b) Clark, R. B.; Pearson, W. H. *Org. Lett.* **1999**, *1*, 349.
16. *7-Phenyl-5,6-dihydroindolizine (**3b**).* Prepared as a yellow solid according to the general procedure starting from **1b** (80% yield). Mp 75°C. ^{1}H NMR δ 7.50–7.15 (m, 5H), 6.83 (s, 1H), 6.62 (s, 1H), 6.15 (m, 2H), 4.07 (t, J=6.9 Hz, 2H), 2.89 (t, J=6.9 Hz, 2H). MS m/e 195 (M^+, 100), 194 (68), 118 (25), 117 (16), 104 (92). Anal. calcd for $C_{14}H_{13}N$: C, 86.15; H, 6.67; N, 7.18. Found: C, 86.70; H, 6.70; N, 7.22. *3-Ethyl-6-methyl-5,6-dihydroindolizine (**3c**).* Prepared as a yellow oil according to the general procedure starting from **1c** (72% yield). ^{1}H NMR δ 6.38 (d, J=9.0 Hz, 1H), 6.18 (d, J=3.2 Hz, 1H), 6.10 (d, J=3.2 Hz, 1H), 5.60 (dd, J=9.0; 3.1 Hz, 1H), 3.52 (d, J=5.0 Hz, 1H), 3.47 (d, J=5.0 Hz, 1H), 2.68 (m, 1H), 2.42 (q, J=7.5 Hz, 2H), 1.25 (t, J=7.5 Hz, 3H), 0.71 (d, J=8.3 Hz, 3H). MS m/e 161 (M^+, 48), 146 (100), 144 (9). Anal. calcd for $C_{11}H_{15}N$: C, 81.99; H, 9.32; N, 8.70. Found: C, 82.30; H, 9.29; N, 8.72. *2-Ethyl-6-methyl-5,6-dihydroindolizine (**3d**).* Prepared as a yellow oil according to the general procedure starting from **1d** (75% yield). The product was eluted with SiO_2; hexane/EtOAc=9:1; ^{1}H NMR δ 6.48 (d, J=2.3 Hz, 1H), 6.40 (d, J=9.0 Hz, 1H), 6.00 (d, J=2.3 Hz, 1H), 5.50 (dd, J=9.0; 3.3 Hz, 1H), 3.92 (dd, J=12.0; 6.4 Hz, 1H), 3.50 (dd, J=12.0; 10 Hz, 1H), 2.75 (m, 1H), 2.46 (q, J=7.5 Hz, 2H), 1.2 (d, J=8.0 Hz, 3H), 1.10 (t, J=7.5 Hz, 3H). MS m/e 161 (M^+, 70), 146 (100), 131 (16), 117 (13). Anal. calcd for $C_{11}H_{15}N$: C, 81.99; H, 9.32; N, 8.70. Found: C, 81.85;

H, 9.28; N, 8.76. *1-Ethyl-6-methyl-5,6-dihydroindolizine (**3′d**).* MS *m/e* 161 (M^+, 72), 146 (100), 131 (20). *5-Methyl-5,6-dihydroindolizine (**3e**).* Prepared as a yellow oil according to the general procedure starting from **1e**. The product was eluted with SiO_2; hexane/EtOAc = 4:1 (62% yield). ^{1}H NMR δ 6.70 (m, 1H), 6.42 (d, J = 9.8 Hz, 1H), 6.14 (m, 1H), 6.03 (m, 1H), 5.65 (m, 1H), 4.10 (m, 1H), 2.53 (m, 1H), 2.20 (m, 1H), 1.43 (d, J = 6.5 Hz, 1H); ^{13}C NMR δ 128.5, 120.1, 118.4, 117.9, 108.0, 106.2, 49.6, 32.2, 20.2. MS *m/e* 133 (M^+, 63), 132 (19), 118 (100), 117 (44), 91 (23). Anal. calcd for $C_9H_{11}N$: C, 81.20; H, 8.27; N, 10.53. Found: C, 81.30; H, 8.21; N, 10.48. The dihydroindolizine **3′d** was characterized via GC–MS analysis in the mixture with the regioisomer **3d**.