Dehydrogenation of 3-Unsubstituted Indolizines on Platinum on Carbon. A Facile Synthesis of Biindolizines

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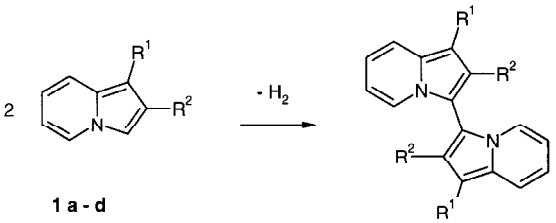
Dedicated to Professor Ernst Schmitz on the occasion of his 70th birthday

Abstract. Biindolizines were synthesised by oxidative dimerisation on platinum on carbon without byproducts in almost quantitative yields.
Key words: indolizines, dimerisation, dehydrogenation on platinum

3,3'-Biindolizines are reversible two-step redox systems of theoretical and practical interest.[2, 3] These connected heteroaromatics as axially chiral compounds[4] are useful tools e.g. in syntheses of cyclophanes[5] or as complex ligands.[6] Several methods for oxidative dimerisation of indolizines unsubstituted at the 3-position have been described in the literature. However, all the known methods have some disadvantages: the coupling of indolizines with potassium ferricyanide is accompanied by a byproduct.[2] The dimerisation of indolizines with Fe^{3+} yielded biindolizines only in some cases.[7] For example the oxidation of the 2-phenylindolizine (**1a**) unsubstituted in 1-position did not take place.



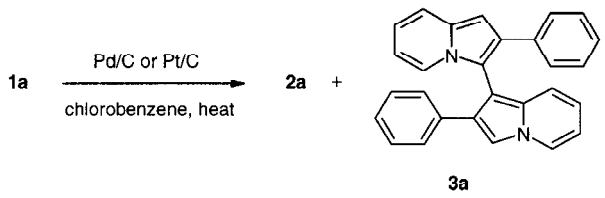
	R^1	R^2
1a / 2a	H	Ph
1b / 2b	H	Me
1c / 2c	Me	Ph
1d / 2d	Me	Me
1e	COOEt	Ph

Scheme 1

The coupling by dehydrogenation on palladium on carbon (Pd/C) under refluxing conditions also allowed the 3,3-dimerisation of indolizines with higher oxidation potentials such as indolizines unsubstituted at the 1-position.[8] For this reason we usually preferred this reaction. But we often obtained, in accordance with literature, yields lower than 40 % by use of *p*-xylene as solvent. Therefore, we were interested in a more detailed investigation of the oxidative coupling reaction depending on the catalyst and/or the presence of oxygen during the reaction.

Our investigations with Pd/C showed a significant increase in yields by the use of higher amounts of catalyst or by bubbling air through the heated mixture.[9] The application of platinum (Pt/C, 10% Pt) instead of palladium on carbon raises the yield of 2,2'-diphenyl-3,3'-biindolizine (**2a)**. The dimer was obtained in 70% yield on bubbling air through the refluxing mixture in chlorobenzene. In contrast to the reaction in the presence of Pd/C only half the amount (0.1 instead of 0.2 equiv.) of catalyst is necessary to obtain a comparable result.

The dimerisation of 2-phenylindolizine under the drastic conditions of 132°C (boiling chlorobenzene) requires a purification of the desired dimer by column chromatography. The time course of the experiments shows high conversion rates only during the starting phase. In all mentioned cases drastic decreases of dimerisation rates are observed after about 25% conversion. As one reason of this limited increase of yields we assumed side reaction. In fact by reaction of 2-phenylindolizine (**1a**) in boiling chlorobenzene on Pd/C as well as on Pt/C a byproduct **3a** was isolated. Since the new compound **3a** shows the same molecular ion in MS as **2a**, we expected an unusual dimerisation involving both the 1- and 3-positions of indolizine.



Scheme 2

The nonsymmetric structure of a 1,3'-dimer was proven by ^{1}H NMR. The spectrum shows two different singlets of the isolated protons in the five-membered fused ring systems. Only one of them is located near to the signal of the hydrogen atom in the 1-position of the symmetric product **2a** at $\delta = 6.91$. The second singlet at $\delta = 8.18$ we assigned to the proton at the 3'-carbon adjacent to the nitrogen. Additional assignments of the ^{1}H-signals were carried out by H,H COSY, HSQC, and HMQC experiments.

The participation of the less reactive 1-position in the reaction indicates drastic reaction conditions. Surprisingly, the dimerisation on platinum on carbon at room temperature (Figure, – ■ –) took place as rapidly as in the starting phase in refluxing chlorobenzene (Figure, – □ –) and led to much higher yields of the dimer than under reflux conditions.

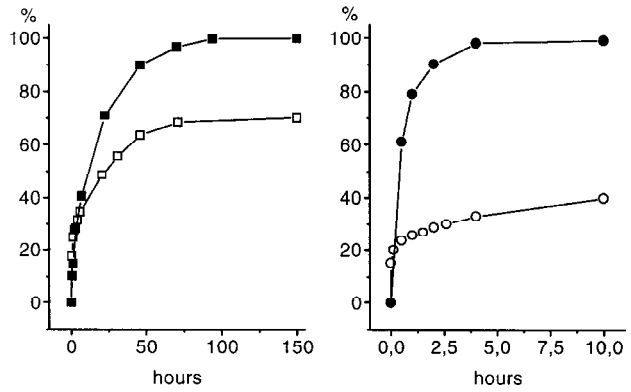


Figure. Dimerisation of 2-phenylindolizine (**1a**) and 1-methyl-2-phenylindolizine (**1c**) with Pt/C in chlorobenzene: left: (– □ –): **1a** refluxing; (– ■ –): **1a** stirring at r.t.; right: (– ● –): **1c** stirring in open vessel; (– ○ –): **1c** stirring under argon.

Under the reaction conditions no byproduct could be detected as shown by HPLC. To confirm the generality of this reaction, we checked the conditions of dimerisation of some indolizines with Pt/C. The results are summarised in the Table. Obviously a relationship exists between the oxidation potential of the indolizines and the rate of dimerisation. With the indolizines tested, those with the lowest oxidation potential **1c** and **1d** needed shorter reaction times. The electron-poor compound 2-phenylindolizine (**1a**) needs the longest reaction time. 1-Ethoxycarbonyl-2-phenylindolizine (**1e**) did not react under the described conditions (see Table).

The corresponding products **2a–d** were obtained from the pale yellow solution by evaporation without separation steps. The slightly varying yields (between 91 and 99%) may be due to different adsorption on the coal-supported catalyst. Lower amounts of the catalyst led to smaller yields. The more reactive 1,2-dimethylindolizine (**1d**) is less sensitive to reduced amounts of Pt/C than the monosubstituted 2-phenylindolizine (**1a**).

To prove the influence of oxygen on the dimerisation of the reactive 1-methyl-2-phenylindolizine (**1c**) the dimerisation was carried out after careful flushing of the flask, the catalyst and the solvents by argon. This consequent exclusion of air during the reaction resulted in a drastic decrease in the rate of reaction. As shown in the Figure (– ○ –) only the first 25 % of monoindolizine **1c** reacts quickly in the starting phase of dimerisation.

Under anaerobic conditions a conversion of 50% was reached only after about 23 hours instead of the few minutes needed in the open system. Obviously, without oxygen inactivation of the catalyst is already observed after a short time. In the following the dehydrogenation by the platinum takes place at slow rates. In the presence of oxygen the potential of oxidation of the catalyst is regenerated to a certain extent. Higher temperatures favour side reactions and give rise to an earlier inactivation of the catalyst in contrast to the reaction at room temperature.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Indolizines **1a–e** were prepared according to literature.[10] Pd, 10% on carbon (Aldrich) and platinum, 10% on carbon (Merck) were used for the experiments. For column chromatography, silica gel Merck KG 60 was used. Mps are uncorrected. NMR spectra were recorded on a Bruker WP 200 SY spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS. Mass spectra were recorded with a Fisons Instruments VG Auto Spec.

Dimerisation; General Procedure:

The reactions were carried out in a open vessel. 1 mmol of the desired indolizine in chlorobenzene (10 mL) was stirred at r.t. with Pt/C (10%, 195 mg, 0.1 mmol). The reaction time is given in the Table. The catalyst was filtered off and the solvent was evaporated under reduced pressure, giving the pure biindolizine. The yields are summarised in the Table.

HPLC check of reactions: The reactions were carried out as described above at r.t. or with heating, in presence of air or by exclusion of oxygen. Loss of solvent by evaporation during the reaction time was replenished by weight. Samples of 0.05 mL were taken at intervals, diluted with MeCN(10 mL) and measured using a LC10-HPLC-system (Shimadzu). The chlorobenzene of the 0.05 mL samples was used as internal standard.

2,2'-Dimethyl-3,3'-biindolizine (2b):

According to the general procedure by stirring of a mixture of 2-methylindolizine (**1b)** (131 mg, 1 mmol) and Pt/C (10%, 195 mg, 0.1 mmol) in chlorobenzene (10 mL).

m/z (EI, high resolution) = 260.13126, $C_{18}H_{16}N_2$.

^{13}C NMR (DMSO-d_6): δ = 12.0 (CH_3), 100.2, 110.1, 111.4, 117.5, 118.4, 122.7, 125.9, 133.0.

^{1}H NMR (DMSO-d_6): δ = 2.07 (s, 6H, CH_3), 6.43–6.48 (m, 2H) 6.48 (s, 2H, H-1/1'), 6.71–6.77 (m, 2H), 7.16 (dd, J = 0.9, 7.0 Hz, 2H), 7.44 (td, J = 1.1, 8.4 Hz, 2H).

Table: Synthesis of Biindolizines in Chlorobenzene–Pt/C at Room Temperature

monomer	dimer	isolated yield/time [%]/[h]	mp [˚C]	mp (Lit) [˚C]	oxidation potential [mV][a]	time for 50% conversion
1a	2,2'-diphenyl-3,3'-biindolizine (**2a**)	94/120	166–168	169–171[7]	0.908	12 h
1b	2,2'-dimethyl-3,3'-biindolizine (**2b**)	91/25	76–78	–	0.813	2.5 h
1c	1,1'-dimethyl-2,2'-diphenyl-3,3'-biindolizine (**2c**)	99/20	242–244	244–246[7]	0.777	25 min
1d	1,1',2,2'-tetramethyl-3,3'-biindolizine (**2d**)	93/20	146–148	144–148[2]	0.640	20 min
1e		0	–	–	1.198	∞

[a] oxidation potential of the compounds **1a–e**, measured by cyclic voltammetry

2,2'-Diphenyl-3,1'-biindolizine (3a):
The compound was obtained as byproduct of **2a** by boiling a solution of 2-phenylindolizine (**1a)** (191 mg, 1 mmol) in chlorobenzene (10 mL) in presence of Pd/C (10%, 212 mg, 0.2 mmol) or Pt/C (10%, 195 mg, 0.1 mmol) for 20 h. Insoluble substances were removed by filtration and the filtrate was concentrated at reduced pressure. The residue was separated by column chromatography on silica gel (heptane/toluene 10:3). **3a** was isolated as an oil in yields of about 5%.
m/z (EI, high resolution) = 384.16320, $C_{28}H_{20}N_2$.
NMR assignments by H,H COSY, HSQC, and HMQC experiments and according to literature.[11]
^{13}C NMR (DMSO-d_6): δ = 98.2 (C-1), 99.1 (C-2'), 110.3 (C-6), 111.2 (C-6'), 112.2 (C-3'), 113.8 (C-2), 116.8 (C-7'), 117.4 (C-7), 118.6 (C-8'), 118.9 (C-8), 122.5 (C-5), 126.5 (C-5'), 125.3, 125.9, 126.1, 126.8, 127.9, 128.3, 128.6, 128.7, 134.6, 135.9 (2 × phenyl, C-3, C-1'); 132.1, 132.4 (8a, 8a').
^{1}H NMR (DMSO-d_6): δ = 6.33 (dt, J = 1.0, 6.8 Hz, 1H, H-6), 6.61–6.65 (m, 2H, H-6', 8'), 6.66–6.71 (m, 2H, H-7, 7'), 6.91 (s, 1H, H-1), 7.05–7.27 (m, 8H, phenyl), 7.31 (dd, J = 1.0, 6.8 Hz, 1H, H-5), 7.36–7.40 (m, 2H, phenyl), 7.47 (d, J = 9.3 Hz, 1H, H-8), 8.18 (s, 1H, H-3'), 8.34–8.38 (m, 1H, H-5').

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