Large Scale Synthesis of 4'-(4-Bromophenyl)-2,2':6',2"-terpyridine and Nature of the Mysterious Green By-product

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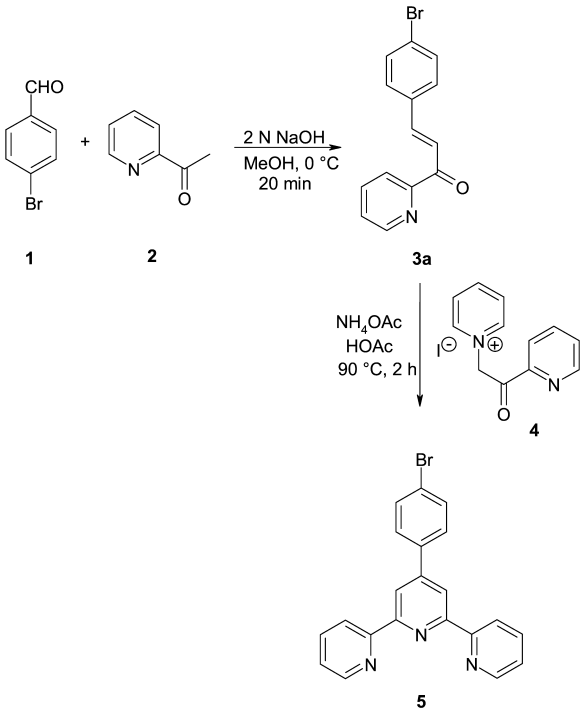
4'-(4-Bromophenyl)-2,2':6',2"-terpyridine (**5**) was prepared on a large scale (up to 100 g batches) from 2-[3-(4-bromophenyl)-1-oxoprop-2-enyl]pyridine (**3a**) and *N*-[2-oxo-2-(2-pyridyl)-ethyl]pyridinium iodide (**4**). In the presence of substoichiometric amounts of **4**, 1-[3-(4-bromophenyl)indolizin-1-yl-1-imino]-3-[4-bromophenyl]-1*H*-indolizinium iodide (**6a**I) was formed as an intensely coloured by-product. The synthesis of several related novel indolizinium derivatives is described, including 1-[3-(4-methylphenyl)indolizin-1-yl-1-imino]-3-[4-methylphenyl]-1*H*-indolizinium hexafluorophosphate (**6c**PF_6), whose crystal structure has been determined.

Key words: Rigid-Rod Molecules, Indolizinium Compounds, X-Ray Data

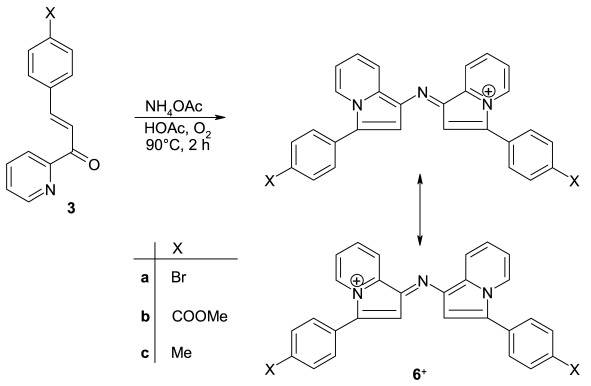
4'-(4-Bromophenyl)-2,2':6',2"-terpyridine (**5**) is a key compound in many studies concerned with metal complexes of rigid-rod type architectures. The compound was first synthesised by Spahni and Calzaferri [1] in 20% yield, employing a one-pot method. We have devised a two-step synthesis, which follows the Kröhnke procedure [2] and gives an overall yield of 55%. Our approach is similar to that recently published by Åkermark and co-workers [3], whose protocol gives a 64% yield, but involves tedious chromatographic purification of the crude product on a very small scale ($\leq$ 1 g). We have used our method to prepare large batches of the compound (up to 100 g), which is obtained in analytically pure form by simple recrystallisation of the crude product (Scheme 1).

If the reaction is performed with substoichiometric amounts of *N*-[2-oxo-2-(2-pyridyl)ethyl]pyridinium iodide (**4**), for example by inadvertently using impure material, an intensely coloured by-product is formed, which can be removed fairly easily owing to its poor solubility in most organic solvents. The solubility of this substance is highest in DMSO, from which it can be recrystallised forming large dark green leaves, which show an impressive metallic lustre. The formation of unidentified by-products of very similar appearance in the synthesis of terpyridines is a common phenomenon and has already been reported by Spahni and Calzaferri [1].



Scheme 1.

We have identified the coloured by-product as the ionic indolizine derivative **6a**I, which results from the reaction of 2-[3-(4-bromophenyl)-1-oxoprop-2-



Scheme 2.

enyl]pyridine (**3a**) with ammonium acetate in the presence of pyridinium iodide, as has been proved by an independent synthesis. Only two examples of related species have been reported to date [4]. They were formed by the reaction of 2-[3-(4-X-phenyl)-1-oxoprop-2-enyl]pyridine (X = Cl, OMe) with ammonium acetate in acetic acid and have been isolated as iodides and perchlorates, when pyridinium iodide and perchlorate, respectively, was present in the reaction mixture, and as acetates in the absence of pyridinium salts. Only very limited data are available for these compounds, which, in a simplified view, may be looked upon as indolizines bearing a substituent NR^+ in the 1-position. Quantum-chemical studies have revealed that such substituted indolizines are most stable when the electron-withdrawing substituent is attached to just this position [5].

We have prepared the new indolizine derivatives **6a**$^+$ – **6c**$^+$ by rational synthesis (isolated as acetates having the stoichiometry **6**OAc•HOAc) (Scheme 2).

We have investigated **6c**$^+$ in some detail, since its solubility is the most favourable. Solutions of this species are intensely blue (λ_{max} = 635 nm, ε = 153000 $M^{-1}\,cm^{-1}$), whereas crystalline salts are dark green or golden green, showing metallic sheen. **6c**OAc•HOAc is very soluble in DMSO and fairly soluble in dichloromethane and hot ethanol. **6c**$^+$ is most conveniently isolated as the chloride salt, which is precipitated by bubbling HCl into a solution of the crude acetate in ethanol or dichloromethane. Since crystals of the acetate and chloride proved notoriously unsuitable for a single-crystal X-ray structure analysis, we synthesised the hexafluorophosphate by stirring a saturated dichloromethane solution of the chloride with an aqueous solution of KPF_6. Single crystals of **6c**PF_6 were grown by cooling of the dried dichloromethane solution and subjected to an X-ray diffraction study. A view of the cation is shown in Fig. 1, representing the first example of a structurally characterised compound of this kind.

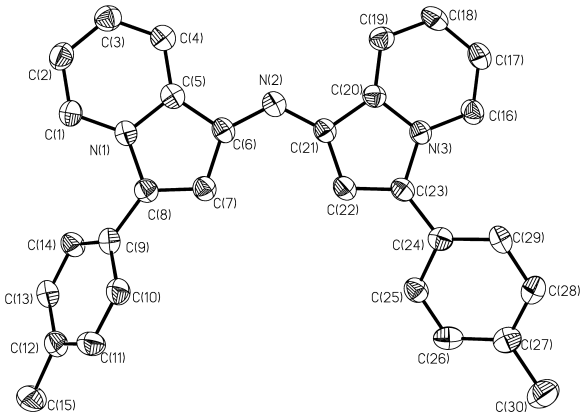


Fig. 1. Molecular structure of the cation of **6c**[PF_6] in the crystal. Selected bond lengths (pm) and angles (°) not mentioned in the text: N(1)-C(1) 1.365(5), N(1)-C(5) 1.389(5), N(1)-C(8) 1.427(5), N(2)-C(6) 1.335(5), N(2)-C(21) 1.337(5), N(3)-C(16) 1.373(5), N(3)-C(20) 1.386(5), N(3)-C(23) 1.428(5), C(1)-C(2) 1.355(6), C(2)-C(3) 1.400(6), C(3)-C(4) 1.366(6), C(4)-C(5) 1.389(6), C(6)-C(7) 1.433(6), C(8)-C(9) 1.464(6), C(16)-C(17) 1.356(6), C(17)-C(18) 1.400(6), C(18)-C(19) 1.375(6), C(19)-C(20) 1.387(6), C(21)-C(22) 1.426(6), C(22)-C(23) 1.371(6), C(23)-C(24) 1.458(6); C(1)-N(1)-C(5) 121.7(4), C(1)-N(1)-C(8) 129.4(4), C(5)-N(1)-C(8) 108.9(3), C(16)-N(3)-C(20) 120.4(3), C(16)-N(3)-C(23) 130.1(4), C(20)-N(3)-C(23) 109.4(3).

The bond lengths in the six-membered heterocycles range from 135.6(6) to 140.0(6) pm and are very similar considering the margin of experimental error. Those in the five-membered rings range from 135.8(6) pm for C(7)–C(8) to 143.5(6) pm for C(5)–C(6) and C(20)–C(21), respectively, and thus show quite significant differences. In comparison to other structurally characterised indolizines, the bonds C(5)–C(6) and C(20)–C(21) are exceptionally long, usual values being in the range of 137 pm [6]. The elongated bonds correspond to a bond order which is lower than usual as is reflected by the resonance structures shown in Scheme 2. The distances between N(2) and the two C atoms attached to it are identical within experimental error (average value 133.6 pm) and correspond to a C–N bond order of 1.5. The angle at N(2) is 125.1(4)°, which is in accord with an sp^2 hybridisation of this atom.

In summary, we have developed a convenient large-batch synthesis of **5**, which is of central importance for studies involving rigid-rod coordination compounds.

We have further elucidated the nature of the mysterious green by- product of the synthesis and have uncovered the reason for its occurrence and the way it can be avoided.

Experimental Section

Compounds **3a** [3], **3c** [7] and **4** [8] were prepared by slight modification of published procedures. All other compounds were commercially available. Solvents were purified by standard procedures. – NMR: Bruker Avance DRX 500 and Varian Unity INOVA 500 (500.13 MHz for ^{1}H). – MS: VG Autospec (EI; LSIMS, 3-nitrobenzyl alcohol matrix). – UV/vis: Perkin Elmer Lambda 9. – Elemental analyses: Beller (Göttingen), H. Kolbe (Mülheim an der Ruhr) and microanalytical laboratory of the University of Bielefeld.

Synthesis of 2-[3-(4-methoxycarbonylphenyl)-1-oxoprop-2-enyl]pyridine (**3b**)

2-Acetylpyridine (**2**) (7.40 g, 61.0 mmol) was added to a solution of methyl 4-formylbenzoate (10.0 g, 61.0 mmol) in methanol (100 ml) cooled to 0 °C. A 2 N solution of sodium hydroxide (100 ml) was added with vigorous stirring. After 14 h at room temperature the yellow precipitate was isolated by filtration, washed with methanol (10 ml) and water (5×50 ml) and dried *in vacuo*. Yield 12.4 g (76%). – ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H), 7.45 – 7.49 (m, 1 H), 7.74 ("d", apparent $J = 8.2$ Hz, 2 H), 7.82 – 7.91 (m, 2 H), 8.03 ("d", apparent $J = 8.2$ Hz, 2 H), 8.15 (d, $J = 7.8$ Hz, 1 H), 8.34 (d, $J = 16.0$ Hz), 8.71 (d, $J = 4.0$ Hz, 1 H). – ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 52.2, 122.9, 123.0, 127.1, 128.5, 130.0, 131.4, 137.0, 139.3, 143.0, 148.9, 153.9, 166.5, 189.2. – MS (EI): *m/z* = 267 [**3b**$^+$]. – $C_{16}H_{13}NO$ (267.3): calcd. C 71.90, H 4.90, N 5.24; found C 71.70, H 5.01, N 5.13.

Synthesis of 4'-(4-bromophenyl)-2,2':6',2"-terpyridine (**5**)

In a typical run, 2-[3-(4-bromophenyl)-1-oxoprop-2-enyl]pyridine (**3a**) (46.7 g, 162.0 mmol), *N*-[2-oxo-2-(2-pyridyl)ethyl)]pyridinium iodide (**4**) (53.0 g, 162.5 mmol) and ammonium acetate (340 g, 4.41 mol) were suspended in acetic acid (600 ml) and heated with stirring to 90 °C for 2 h. The mixture was allowed to cool to room temperature with stirring, affording the product as colourless needles, which were filtered off, washed with water and dried *in vacuo*. Yield 34.8 g (55%). The reaction may be scaled up by at least a factor of two without a decrease of the yield. – ^{1}H NMR ($CDCl_3$): δ = 7.32 – 7.37 (m, 2 H), 7.61 ("d", apparent $J = 8.6$ Hz, 2 H), 7.75 ("d", apparent $J = 8.6$ Hz, 2 H), 7.83 – 7.89 (m, 2 H), 8.63 (d, $J = 8.6$ Hz, 2 H), 8.66 (s, 2 H), 8.71 (d, $J = 4.2$ Hz, 2 H). – ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 118.5, 121.3, 123.4, 123.9, 128.9, 132.1, 136.9, 137.4, 149.0, 149.1, 156.0. – MS (EI): *m/z* (%) = 389 (97) [**5**$^+$ (^{81}Br)], 387 (100) [**5**$^+$ (^{79}Br)]. – $C_{21}H_{14}BrN_3$ (388.3): calcd. C 64.96, H 3.63, N 10.82; found C 64.47, H 3.82, N 10.79.

Synthesis of 1-[3-(4-bromophenyl)indolizin-1-yl-1-imino]-3-(4-bromophenyl)-1H-indolizinium acetate (**6aOAc • HOAc**)

A suspension of **3a** (14.0 g, 46.6 mmol) and ammonium acetate (23.0 g, 298 mmol) in acetic acid (100 ml) was slowly heated to 100 °C. After 10 min at this temperature the dark blue solution was allowed to cool to room temperature. The product was isolated by filtration, washed with diethyl ether (3×20 ml) and dried *in vacuo*. Yield 13.5 g (82%). – ^{1}H NMR (DMSO-d_6): $\delta = 1.75$ (s, 6 H), 7.54 (m, 2 H), 7.79 ("d", apparent $J = 8.5$ Hz, 4 H), 7.86 ("d", apparent $J = 8.5$ Hz, 4 H), 8.00 (s, 2 H), 8.05 (m, 2 H), 8.55 ("d", apparent $J = 8.4$ Hz, 2 H), 8.79 ("d", apparent $J = 6.6$ Hz, 2 H), 13.69 (br. s, 1 H). – ^{13}C{^{1}H} NMR (DMSO-d_6): $\delta = 21.6$, 113.5, 122.0, 123.6, 126.7, 130.0, 133.1, 134.2, 135.3, 137.5, 138.3, 142.8, 146.1, 176.6. – MS (LSIMS): *m/z* = 556 [**6a**$^+$]. – $C_{32}H_{25}N_3Br_2O_4$ (675.4): calcd. C 56.91, H 3.73, N 6.22; found: C 57.13, H 3.92, N 6.01.

Synthesis of 1-[3-(4-bromophenyl)indolizin-1-yl-1-imino]-3-(4-bromophenyl)-1H-indolizinium iodide (**6aI**)

A solution of **6a**OAc•HOAc (1.00 g, 1.48 mmol) and pyridinium iodide (310 mg, 1.50 mmol) in ethanol (10 ml) was heated to reflux for 2 h. The mixture was allowed to cool to room temperature. The product was isolated by filtration and dried *in vacuo*. Yield 935 mg (83%). Alternatively, the product may be obtained in similar yield from the reaction of **3a** with ammonium acetate in the presence of pyridinium iodide. An analytical sample was obtained by recrystallisation from DMSO and had the composition **6a**I•DMSO. – ^{1}H NMR (DMSO-d_6): $\delta = 7.54$ (m, 2 H), 7.79 ("d", apparent $J = 8.5$ Hz, 4 H), 7.86 ("d", apparent $J = 8.5$ Hz, 4 H), 8.00 (s, 2 H), 8.05 (m, 2 H), 8.55 ("d", apparent $J = 8.4$ Hz, 2 H), 8.79 ("d", apparent $J = 6.6$ Hz, 2 H). – ^{13}C{^{1}H} NMR (DMSO-d_6): $\delta = 113.5$, 122.0, 123.6, 126.7, 130.0, 133.1, 134.2, 135.3, 137.5, 138.3, 142.8, 146.1. – MS (LSIMS): *m/z* = 556 [**6a**$^+$]. – $C_{30}H_{24}N_3Br_2IOS$ (761.3): calcd. C 47.32, H 3.18, N 5.74, Br 20.99, I 16.67, O 2.10, S 4.21; found: C 46.91, H 3.31, N 5.74, Br 21.13, I 16.90, O 2.32, S 4.28.

Synthesis of 1-[3-(4-methoxycarbonylphenyl)indolizin-1-yl-1-imino]-3-(4-methoxycarbonylphenyl)-1H-indolizinium iodide (**6bOAc • HOAc**)

By a procedure analogous to that described for **6a**OAc•HOAc, 17.3 g (56%) of **6b**OAc•HOAc was obtained from the reaction of **3b** (13.0 g, 48.6 mmol) and ammonium acetate (23.0 g, 300 mmol) in acetic acid (100 ml). Owing

to the poor solubility of the product, no interpretable NMR spectra could be obtained. – MS (LSIMS): *m/z* = 514 [**6b**$^+$]. – $C_{36}H_{31}N_3O_8$ (633.7): calcd. C 68.23, H 4.93, N 6.63; found C 68.33, H 5.25, N 6.86.

Synthesis of 1-[3-(4-methylphenyl)indolizin-1-yl-1-imino]-3-(4-methoxycarbonylphenyl)-1H-indolizinium acetate (**6cOAc • HOAc**)

By a procedure analogous to that described for **6a**OAc•HOAc, 13.7 g (83%) of **6c**OAc•HOAc was obtained from the reaction of **3c** (13.5 g, 60.5 mmol) and ammonium acetate (20.0 g, 359 mmol) in acetic acid (90 ml). – ^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 6 H), 2.42 (s, 6 H), 7.22 (s, 2 H), 7.35 ("d", apparent J = 7.7 Hz, 4 H), 7.45 (m, 2 H), 7.48 ("d", apparent J = 7.9 Hz, 4 H), 7.91 (m, 2 H), 8.37 (d, J = 8.3 Hz, 2 H), 8.50 (d, J = 6.5 Hz, 2 H). – ^{13}C{^{1}H} NMR (DMSO-d_6): δ = 21.6, 22.9, 109.2, 119.6, 120.2, 124.0, 128.2, 128.4, 130.2, 134.6, 140.9, 141.1, 143.1, 176.4. – MS (LSIMS): *m/z* = 426 [**6c**$^+$]. – $C_{34}H_{31}N_3O_4$ (545.6): calcd. C 74.84, H 5.73, N 7.70; found: C 75.00, H 6.03, N 7.71.

Synthesis of 1-[3-(4-methylphenyl)indolizin-1-yl-1-imino]-3-(4-methylphenyl)-1H-indolizinium chloride (**6cCl • 2H$_2$O**)

A suspension of **3c** (13.5 g, 60.5 mmol) and ammonium acetate (20.0 g, 259 mmol) in acetic acid (90 ml) was slowly heated to 100 °C. After 10 min at this temperature the dark blue solution was allowed to cool to room temperature. Dichloromethane (100 ml) was added and subsequently water (200 ml). The organic layer was separated and dried with sodium sulfate. HCl was bubbled through the solution. The product was isolated by filtration, washed with ethanol (10 ml) and water (2 × 10 ml) and dried *in vacuo*. Yield 8.42 g (76%). – ^{1}H NMR (DMSO-d_6): δ = 2.43 (s, 6 H), 3.61 (s, 4 H), 7.44 ("d", apparent J = 7.7 Hz, 4 H), 7.49 (m, 2 H), 7.69 ("d", apparent J = 7.7, 4 H), 7.89 (s, 2 H), 8.00 (m, 2 H), 8.47 (d, J = 8.3 Hz, 2 H), 8.73 (d, J = 6.4 Hz, 2 H). – ^{13}C{^{1}H} NMR (DMSO-d_6): δ = 21.0, 109.7, 118.9, 120.3, 124.8, 128.9, 129.7, 134.4, 134.8, 140.0, 142.9. – MS (LSIMS): *m/z* = 426 [**6c**$^+$]. – $C_{30}H_{28}N_3ClO_2$ (498.0): calcd. C 72.35, H 5.67, N 8.44; found: C 71.95, H 5.92, N 8.82.

Synthesis of 1-[3-(4-methylphenyl)indolizin-1-yl-1-imino]-3-(4- methylphenyl)-1H-indolizinium hexafluorophosphate (**6c**PF_6)

A saturated aqueous solution of potassium hexafluorophosphate (10 ml) was added to a saturated solution of **6c**Cl•2H_2O in dichloromethane (10 ml). The mixture was stirred vigorously for 1 h. The organic layer was separated and dried with sodium sulfate. Crystallisation at 4 °C afforded a small amount of the product as dark green needles. The compound was characterised by single-crystal X-ray diffraction.

Crystal structure determination of compound **6cPF$_6$ • CH$_2$Cl$_2$**

Siemens P2$_1$ four-circle diffractometer, graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Structure solution by direct methods; full-matrix least-squares refinement on F^2 (Siemens SHELXTL PLUS, SHELXL 97). $C_{31}H_{26}Cl_2F_6N_3P$ (656.42), monoclinic, space group $P2_1/n$, a = 8.365(2), b = 19.955(4), c = 17.520(5) Å, β = 97.31(2), V = 2900.7(12) Å^3, Z = 4, d_{calcd} = 1.503 g/cm^3, μ = 0.346 mm^{-1}, $F(000)$ = 1344. A metallic-green needle (0.7 × 0.2 × 0.2 mm^3) was used for data collection at 173 K. θ Range 2.0 – 25.0°, $0 \le h \le 9$, $0 \le k \le 23$, $-20 \le l \le 20$; 5463 reflections collected, 5090 independent (R_{int} = 0.0423); no absorption correction was applied; 389 parameters; no restraints. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at calculated positions using a riding model. Final $R1$ = 0.0622, $wR2$ = 0.1560. Residual electron density: 0.287/−0.376 e/Å^3. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC-192341. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int.code+(1223)336-033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk].

[1] W. Spahni, G. Calzaferri, Helv. Chim. Acta **67**, 450 (1984).
[2] F. Kröhnke, Synthesis 1 (1976).
[3] P. Korall, A. Börje, P.-O. Norrby, B. Åkermark, Acta Chem. Scand. **51**, 760 (1997).
[4] F. W. Kröck, F. Kröhnke, Chem. Ber. **104**, 1645 (1971).
[5] D. A. Maiboroda, E. V. Babaev, K. Jug, J. Org. Chem. **62**, 7100 (1997).
[6] T. L. Gilchrist, Heterocyclenchemie, p. 16, VCH, Weinheim (1995).
[7] C. Mikel, P. G. Potvin, Inorg. Chim. Acta **325**, 1 (2001).
[8] G. U. Priimov, P. Moore, P. K. Maritim, P. K. Butalanyi, N. W. Alcock, J. Chem. Soc., Dalton Trans. 445 (2000).