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Iodine – Sodium Acetate (I_2–NaOAc) mediated oxidative dimerization of indolizines: an efficient method for the synthesis of biindolizines

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Abstract: An I_2–NaOAc mediated one-pot process for the oxidative dimerization of indolizines under mild conditions is described. The reaction afforded a variety of products in good to excellent yields from indolizines with acceptor groups. Macrocyclic systems with the biindolizine fragment(s) were also synthesized from monoindolizinylquinoxaline podands under the same conditions.

Keywords: Indolizines, I_2–NaOAc; Oxidative dimerization; 3,3′-Biindolizines; Indolizine macrocycles; Quinoxaline macrocycles; X-ray analysis

3,3′-Biindolizines are reversible two-step redox systems of theoretical and practical interest, which have attracted attention as an organic electroluminescent device,[1] as a structural unit of cyclophanes,[2] as redox active and luminescent materials[3] and as chiral ligands.[4] Methods for the synthesis of biindolizines have been developed only with substrates containing electron-donating groups in good yields, using various agents including $K_3[Fe(CN)_6]$,[5] Pd/C,[6] Pt/C[6d] and Fe (III)/O_2.[7] Indolizines with acceptor substituents either did not undergo oxidation,[6d] or the yields were very low[2a,6d,7] as in the cases with heteroaryl substitutents. A new method for the oxidative dimerization of indolizines when exposed to $Pd(OAc)_2$[8] was reported to produce high yields of biindolizines, including examples with an acceptor substituent at position 1. Molecular iodine has received considerable attention in organic synthesis because of its low cost and ready availability. The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis for performing several organic transformations with stoichiometric to catalytic amounts.[9] However, there are no examples in which molecular iodine serves as a mild oxidant for the transformation of indolizine → biindolizine. However, it should be noted that molecular iodine has been used as an excellent reagent-catalyst for the synthesis of indolizine derivatives via 5-*endo*-*dig* cyclization.[10] The application of molecular iodine for the dehydrogenation of indolizines should, on the one hand, remove the need for a catalyst or toxic reagents, while on the other hand, make it possible to carry out the desired reaction under mild conditions, *i.e*. at room temperature and with easily removable solvents such as methylene chloride.

In accordance with our interest in developing indolizine chemistry,[3b,c,11a,b] herein we report efficient and convenient approaches to the oxidative dimerization of indolizines, with acceptor substituents such as a quinoxalin-3-yl fragment or an ester group at position 2, using both molecular iodine and the binary system of molecular iodine and NaOAc (I_2–NaOAc). These new methods are applied for synthesizing macrocycles, which, owing to the biindolizine system in their structures are promising redox switchable ligands and redox active materials.[2,4]

As can be seen from Table 1, the reactions of indolizines **1a,b**[11a] containing a 1-alkylquinoxalin-3-yl substituent at position 2, as an acceptor group, with a 1.5 fold excess of molecular iodine for 20 hours led to the formation of biindolizines **2a,b** in good yields. It should be pointed out that independent of the reaction time (24 or 48 h) and the ratio of the reagents, a two or three fold excess of molecular iodine was used; along with the desired biindolizines **2a,b**, ~10-15% of the starting material(s) remained in the reaction mixture. An appreciable increase in yields (~15%) occurred when the binary system (I_2–NaOAc) was used instead of molecular iodine alone.[12]

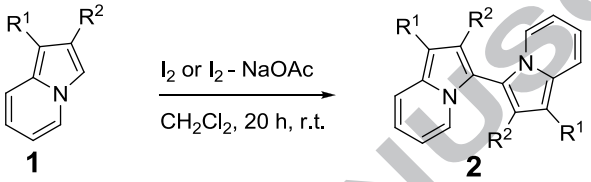
The most notable effect of the use of the binary system (I_2–NaOAc) was achieved by the oxidative dimerization of indolizine **1c** possessing a bromodecyl fragment. Decomposition of compound **1c** occurred when it was stirred with molecular iodine at room temperature in CH_2Cl_2 for 20 hours, the desired product **2c** being isolated in only a trace amount. When the binary system (I_2–NaOAc) was used, the desired product **2c** was obtained in 80% yield after 30 minutes.[13]

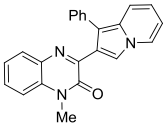
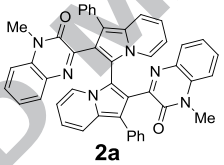
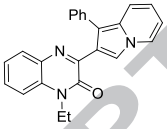
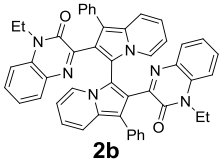
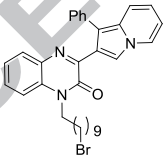
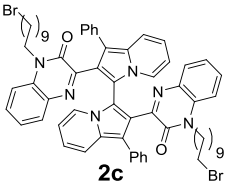
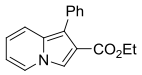
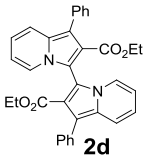
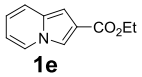
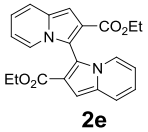
The oxidative dimerization of 1-phenyl-2-ethoxycarbonylindolizine (**1d**), using the binary oxidation system (I_2 + NaOAc) gave a dimer **2d** in 90% yield (Table 1). In contrast, it should be emphasized that the presence of the ethoxycarbonyl group as an acceptor group in 1-ethoxycarbonyl-2-phenylindolizine (which is the isomer of the indolizine **1d**) did not lead to formation of the corresponding dimer in the presence of Pd/C.[6d] The absence of a phenyl substituent at position 1 did not prevent application of the I_2-NaOAc system for the synthesis of 2,2′-biindolizines with the free 1,1′-CH groups. In the presence of a 1.5 fold excess of molecular iodine the predominant product of the oxidation of compound **1e** was tetramer **3**, formed in 18% yield. In this case, the yield of dimer **2e** was 10%. On decreasing the excess of the molecular iodine to 1.1 equivalents there remained a significant amount of unreacted indolizine **1e**. The use of the binary oxidation system I_2-NaOAc with a 1.35 fold excess of iodine made it possible to obtain dimer **2e** in 45% yield. The yield of the tetramer **3** in this case was 4% (Table 1).

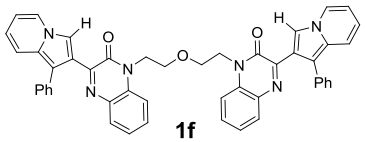
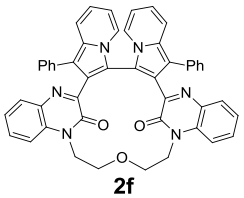
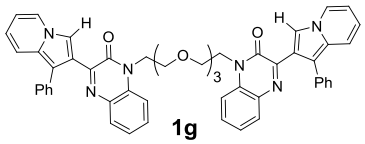
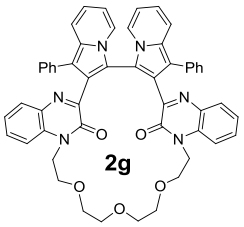
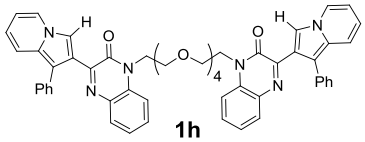
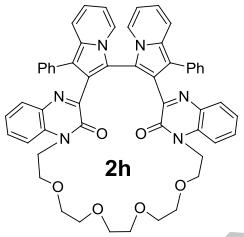
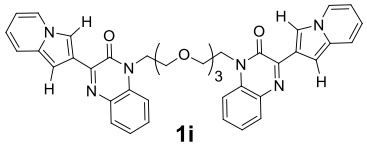
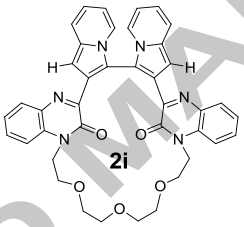
When exposed to the I_2–NaOAc binary system, compounds with two indolizine fragments, **1f-h**[11a] successfully underwent intramolecular cyclization with the formation of macrocycles **2f-h**[12] in high yields (Table 1). In addition, the macrocyclization of podands **1g,h** gave products **2g,h** in high yields using molecular iodine. The use of molecular iodine for the oxidation of podand **1f** gave

macrocycle **2f (**of smaller size) in a moderate yield. In this case, there appeared to be products of oligomerization in the reaction mixture and a significant amount of the starting substrate **1f** remained. Application of the binary system (I_2–NaOAc) increased the yield of macrocycle **2f** up to 60%, the macrocyclic dimer **4** was obtained in a 24% yield. Decreasing the excess of molecular iodine from a 2.3-fold excess to a two fold excess in the case of a podand **1i**, it was possible to synthesize the macrocycle **2i** with the free 1,1′-CH groups, via the regioselective oxidative coupling of the 3,3′-CH groups of the 2,2′-biindolizine system.

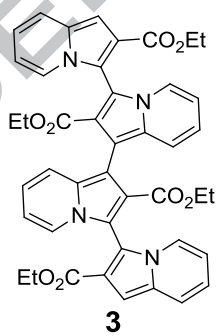
Table 1. Iodine-mediated oxidation of indolizines **1** to biindolizines **2**



Entry	Substrate	Product	mp (°C)	Yield of **2** (%)		R_f
				I_2	I_2-NaOAc	
1	 **1a**	 **2a**	317-319	70	83	0.18[d]
2	 **1b**	 **2b**	303-305	73	92	0.40[d]
3	 **1c**	 **2c**	172-174	5	80[a]	0.45[e]
4	 **1d**	 **2d**	132-134	-	90	0.58[e]
5	 **1e**	 **2e**	170-171	-	45[b]	0.55[e]
6			>360	35	60[c]	0.12,[f] 0.48[g]

	 **1f**	 **2f**				
7	 **1g**	 **2g**	>360	69	92	0.18[f]
8	 **1h**	 **2h**	309-311	75	86	0.07[g]
9	 **1i**	 **2i**	>360	-	50	0.24[g]

[a] Reaction was carried out for 30 min with the addition of molecular I_2 in three stages.[13]
[b] Along with the dimer **2e** a tetramer **3** (Figure 1) was obtained in 4% yield, m.p. 214-216 °C, R_f 0.19.[e]
[c] Along with a macrocycle **2f**, dimer **4** (Figure 1) was obtained in 24% yield, m.p. 265-267 °C, R_f 0.92.[f]
[d] EtOAc/hexane = 1:2; [e] EtOAc/hexane = 1:3; [f] EtOAc/hexane = 3:2; [g] EtOAc.


3

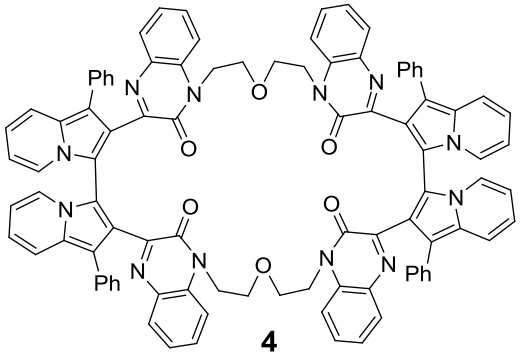

4

Figure 1. Compounds **3** and **4** – the products of the tetramerization and dimerization of compounds **1e** and **1f**, respectively.

The absence of singlet signals for the H3 protons of the indolizine fragments in the ^{1}H NMR spectra at 7.8-8.5 ppm points to the fact that the oxidative dimerization had occurred with the formation of dimers **2a-e** in the cases of compounds **1a-e**, and macrocycles **2f-i** in cases of compounds

1f-i. In the latter cases the ring formation occurred at the C3-C3′ carbon atoms of the indolizines.[12] The mass spectra (MALDI) of these compounds displayed ion peaks at appropriate $[MH]^+$ values.[12,13]

The molecular structures of dimers **2d, 2e**, tetramer **3** and macrocycle **2i** were confirmed unambiguously by single-crystal X-ray analyses (Figures 2-5).[14-18]

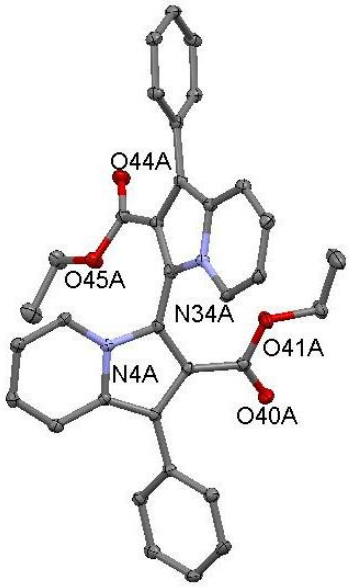


Figure 2. ORTEP plot of compound **2d** and partial numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are omitted for clarity.

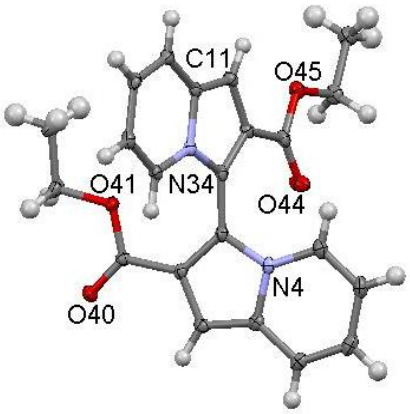


Figure 3. ORTEP plot of compound **2e** and partial numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are represented by circles of an arbitrary size. Crystals of **2e** appeared to be a solid solution. That is, two different molecules were present in the crystal of **2e**: one type with a hydrogen atom at the C(11) position (relative occupancy is 0.88), and another type with a chlorine atom at the C(11) position (relative occupancy is 0.12). In this figure only the molecule with a hydrogen atom at the C(11) position (with maximum occupancy 0.88) is shown.

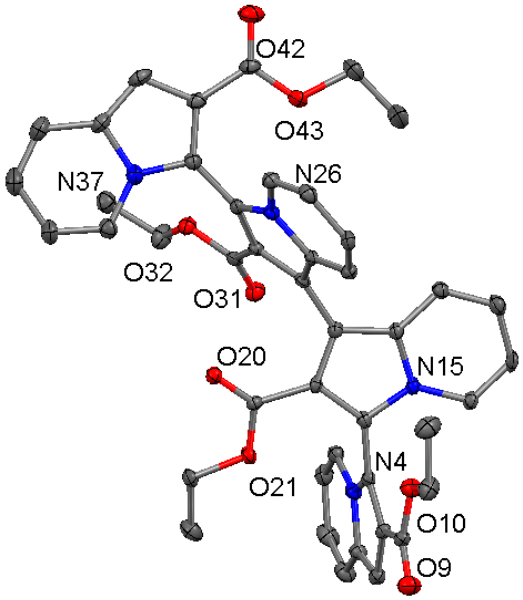


Figure 4. ORTEP plot of compound **3** and partial numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are omitted for clarity.

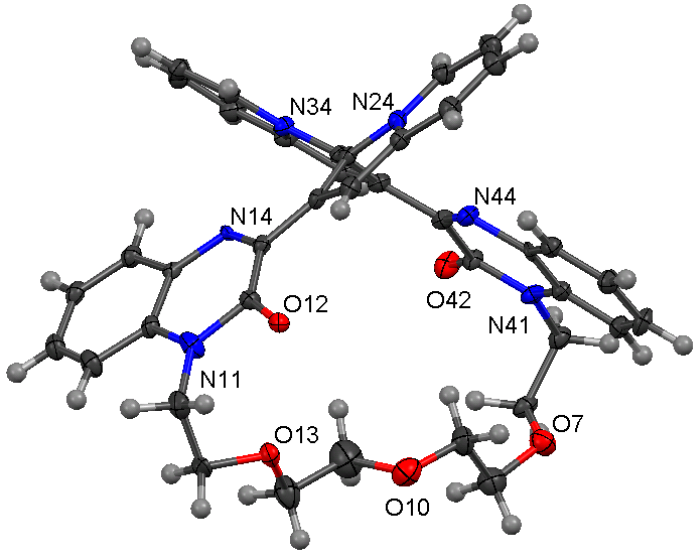


Figure 5. ORTEP plot of compound **2i** and partial numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by circles of arbitrary size.

In conclusion, we have reported a highly efficient method for the synthesis of biindolizines, including macrocyclic systems with biindolizine fragment(s) from indolizines and monoindolizinylquinoxaline podands with acceptor groups, using molecular iodine or the binary I_2–NaOAc reagent system. The present approach carried out under extremely mild conditions provides a novel and efficient synthesis of biindolizine derivatives. The reagent employed for this process is

inexpensive, odorless and nontoxic, making this a practical protocol. Further investigations of the scope and limitations of these reactions are in progress in our laboratory.

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12 *General procedure for the synthesis of 3,3′-biindolizines (**2a,b,d,e**) and 2^1,3^1-diphenyl-1^2,4^2-dioxo-1,4(3,1)-diquinoxalina-2(2,3),3(3,2)-diindolizinacycloalkaphanes (**2f-i**)*. A solution of I_2 (0.12 g, 0.47 mmol) in CH_2Cl_2 (20 ml) at room temperature was added to a stirred mixture of the appropriate indolizine **1** (0.32 mmol for **a,b,d**; 0.36 mmol for **e**; 0.2 mmol for **f-h**; 0.24 mmol for **i**) and NaOAc (39 mg, 0.47 mmol) in CH_2Cl_2 (20 ml for **a,b,d,e**; 140 ml for **f-i**). After being stirred for 20 h at rt, the reaction mixture was washed with aqueous $NaHCO_3$ and $Na_2S_2O_3$. The organic

layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexanes-CH_2Cl_2 = 7:3→CH_2Cl_2-EtOH = 50:1) to give compound **2**. Compound **2h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20-3.45 (m, 16H), 3.80-3.92 (m, 2H), 3.92-4.04 (m, 2H), 6.64 (2H, ddd, *J* = 7.2, 6.8, 0.9 Hz, H6-ind), 6.86 (2H, ddd, *J* = 8.9, 6.8, 0.7 Hz, H7-ind), 7.05-7.42 (18H, m, ArH), 7.62 (2H, d, *J* = 6.8 Hz, H5-ind), 7.70 (2H, d, *J* = 9.2 Hz, H8-ind). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 42.00, 67.79, 70.32, 70.86, 70.88, 111.79, 114.17, 114.36, 115.29, 118.40, 118.92, 122.50, 124.35, 125.37, 125.96, 128.04, 129.26, 129.59, 130.09, 130.99, 133.19, 133.58, 135.57, 153.61, 153.68. IR (ν_{max}, cm^{-1}, KBr): 3072, 2923, 2868, 1654, 1602, 1583, 1529, 1520, 1488, 1444, 1363, 1347, 1308, 1278, 1424, 1125, 768, 727, 700, 608, 560, 507, 434 cm^{-1}. MS (MALDI) 875 $(MH)^+$, 897 $(M+Na)^+$, 913 $(M+K)^+$. Found: C, 74.04; H, 5.17; N, 9.65. $C_{54}H_{46}N_6O_6$ requires: C, 74.13; H, 5.30; N, 9.60.

13 *Procedure for the synthesis of 1,1′-diphenyl-2,2′-di[5-(10-bromodecyl)quinoxalin-2-on-3-yl]-3,3′-biindolizine (**2c**):* A solution of I_2 (0.40 g 1.6 mmol) in CH_2Cl_2 (9 ml) at room temperature was added to a stirred suspension of the indolizine **1c** (0.62 g, 1.1 mmol) and NaOAc (0.18 g, 2.2 mmol) in CH_2Cl_2 (30 ml) 20 min, in three times every 10 min per 3 mL. The reaction mixture was stirred 10 min at this temperature and then was washed with aqueous 5% $NaHCO_3$ (10 mL) and 5% $Na_2S_2O_3$ (10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography with 3:1→2:1 hexane : CH_2Cl_2 to give compound **2c**. Yellow powder, mp 172-174 ^{o}C. IR (ν_{max}, cm^{-1}, Nujol mull): 1653, 1602, 1585, 1548, 1348, 1307, 1279, 1159, 1103, 1075, 972, 74, 722. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.15-1.30 (20H, m, CH_2), 1.35-1.45 (8H, m, CH_2), 1.80-1.90 (4H, m, CH_2), 3.40 (4H, t, *J* = 6.9 Hz, CH_2Br), 3.62-3.72 (2H, m, NCH_2), 3.90-4.00 (2H, m, NCH_2), 6.61-6.68 (2H, m, H6-ind), 6.82-6.89 (2H, m, H7-ind), 6.94 (2H, dd, *J* = 7.6, 7.2 Hz, H6-quin), 7.00 (2H, d, *J* = 7.4 Hz, H5-quin), 7.07 (2H, dd, *J* = 8.4 Hz, H8-quin), 7.11 (2H, dd, *J* = 7.5, 7.5 Hz, *p*-Ph), 7.22 (4H, dd, *J* = 7.8, 7.5 Hz, *m*-Ph), 7.32 (2H, d, *J* = 8.4, 6.9, 1.7 Hz, H7-qui), 7.40 (4H, d, *J* = 7.5 Hz, *o*-Ph), 7.64-7.70 (4H, m, H5,8-ind). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.05, 27.22, 28.52, 29.05, 29.50, 29.63, 29.72, 33.19, 34.33, 42.28, 112.18, 113.37, 115.11, 115.71, 118.78, 119.19, 122.91, 124.93, 125.78, 125.90, 128.29, 129.68, 130.23, 130.31, 131.55, 132.92, 133.37, 135.75, 153.76, 154.00. MS (MALDI TOF) = 1113, 1111, 1109 $(MH)^+$. Found: C, 69.07; H, 5.90; N, 7.57; Br, 14.28. $C_{64}H_{66}N_6O_2Br_2$ requires: C, 69.19; H, 5.99; N, 7.56; Br, 14.38.

14 The X-ray diffraction data for crystals of **2d** were collected on a Bruker AXS Smart APEX II CCD diffractometer at 296 K. *Crystallographic data* for **2d**. $C_{34}H_{28}N_2O_4$, colorless prisms, formula weight 528.58, monoclinic, *P 2$_1$/c*, *a* = 14.296(1) Å, *b* = 34.083(4) Å, *c* = 16.876(2) Å, β = 93.291(2)º, *V* = 8209(1) Å^3, *Z* = 12 (three independent molecules), ρ_{calc} = 1.283 g cm^{-3}, $\mu(\lambda MoK_\alpha)$ = 0.84 cm^{-1}, F(000) = 3336, reflections collected = 62140, unique = 16100, $R_{(int)}$ = 0.1110, full matrix least squares on F^2, parameters = 1088, restraints = 0. Final indices R_1 = 0.0569, wR_2 = 0.1057 for 8765 reflections with I > 2σ(*I*); R_1 = 0.1265, wR_2 = 0.1327 for all data, goodness-of-fit on F^2 = 0.974, largest difference in peak and hole (0.260 and –0.273 *e*Å^{-3}).

15 The X-ray diffraction data for crystals of **2e** was collected on a Bruker AXS Smart APEX II CCD diffractometer at 296 K. *Crystallographic data* for **2e**. $C_{22}H_{21}N_2O_4$(88%) · $C_{22}H_{20}ClN_2O_4$(12%), colorless prisms, formula weight 376.40, monoclinic, *P 2$_1$/c*, *a* = 10.534(2) Å, *b* = 15.189(2) Å, *c* = 14.744(2) Å, β = 128.322(7)º, *V* = 1851.0(5) Å^3, *Z* = 4, ρ_{calc} = 1.351 g cm^{-3}, $\mu(\lambda MoK_\alpha)$ = 0.94 cm^{-1}, F(000) = 792, reflections collected = 13659, unique = 3631, $R_{(int)}$ = 0.0255, full matrix least squares on F^2, parameters = 269, restraints = 0. Final indices R_1 = 0.0532, wR_2 = 0.1219 for 3270 reflections with I > 2σ(*I*); R_1 = 0.0583, wR_2 = 0.1244 for all data, goodness-of-fit on F^2 = 1.153, largest difference in peak and hole (0.765 and – 0.503 *e*Å^{-3}).

16 The X-ray diffraction data for crystals of **3** were collected on a Smart Apex II CCD diffractometer at 100(2) K. *Crystallographic data* for **3**. $C_{44}H_{38}N_4O_8$, colourless plate crystals, formula weight 750.78, triclinic, P-1, a = 7.932(4), b = 14.747(6), c = 17.614(8)Å, α = 66.632(5)°, β = 86.199(5)°, γ = 83.562(6)°, V = 1879(1) Å^3, Z = 2, ρ_{calc} = 1.327 g·cm^{-3}, $\mu(\lambda Mo\ K_\alpha)$= 0.092 mm^{-1}. *F*(000) = 788, reflections collected = 15249, unique = 7610, R(int) = 0.0839, full-matrix least-squares on F^2,

parameters = 510, restraints = 0. Final indices R_1 = 0.0816, wR_2 = 0.1863 for 3475 reflections with I>2σ(I); R_1 = 0.1884, wR_2 = 0.2348 for all data, goodness-of-fit on F^2 = 0.977, largest difference in peak and hole (2.128 and -0.082e $Å^{-3}$).

17 The X-ray diffraction data for crystals of **2i** were collected on a Smart Apex II CCD diffractometer at 150(2) K. *Crystallographic data* for **2i**.. $C_{40}H_{34}N_6O_5$, red prismatic crystals, formula weight 678.73, monoclinic, P 2_1/n, a = 14.999(3), b = 15.213(3), c = 15.854(4)Å, β = 112.988(3)°, V = 3330(1) $Å^3$, Z = 4, ρ_{calc} = 1.354 g·cm^{-3}, μ(λMo K_α)= 0.091 mm^{-1}. *F*(000) = 1424, reflections collected = 49480, unique = 7988, R(int) = 0.0669, full-matrix least-squares on F^2, parameters = 650, restraints = 38. Final indices R_1 = 0.0578, wR_2 = 0.1160 for 5055 reflections with I>2σ(I); R_1 = 0.1054, wR_2 = 0.1336 for all data, goodness-of-fit on F^2 = 1.038, largest difference in peak and hole (0.250 and -0.247e $Å^{-3}$).

18 Crystallographic data (excluding structure factors) for have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 923523, 923524, 922447 and 922448 (compounds **2d**, **2e**, **3** and **2i**, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Graphical abstract

Iodine – Sodium Acetate (I_2–NaOAc) mediated oxidative dimerization of indolizines: an efficient method for the synthesis of biindolizines

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