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Tetrahedron Letters 49 (2008) 3300–3303
Tetrahedron Letters

First synthesis and electronic properties of cyano(oligo)phenothiazines

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Received 17 January 2008; revised 4 March 2008; accepted 14 March 2008
Available online 19 March 2008

Abstract

(Oligo)phenothiazinyl nitriles were synthesized in good to very good yields from bromo (oligo)phenothiazines via the Beller cyanation protocol either under conductive or under dielectric heating using NMP as a solvent. Their electronic properties were determined by absorption and emission spectroscopy and cyclic voltammetry. Cyano(oligo)phenothiazines display large Stokes-shifts (5800–8300 cm^{-1}) and substantial quantum yields (11–27%). Their reversible oxidation potentials are considerably shifted anodically due to the electron-withdrawing character of the cyano group.

Keywords: Cyanation; Palladium; Phenothiazine; Microwave chemistry; Cyclovoltammetry; Fluorescence

Aromatic nitriles are important intermediates for many synthetic targets such as dyes, natural products, herbicides and pharmaceuticals.[1] Their transformation potential into other functional groups opens avenues to nitrogen-containing heterocycles such as tetrazoles, oxazoles, thiazoles or oxazolidines. Methods for the conversion of aryl halides to the corresponding nitriles are legion,[2] and among them the copper-promoted Rosenmund–von Braun reaction is of significant importance, although copper-catalyzed versions are known as well.[3] Besides copper salts, the use of nickel[4] or palladium[5] complexes as cyanation catalysts and alkali and transition metal cyanides, trimethylsilyl cyanide and acetone cyanohydrin as cyanide sources have become common.[6] However, the use of potassium hexacyano-ferrate $K_4[Fe(CN)_6]$ as a source of cyanide has been shown by Beller to combine excellent efficiency with low palladium catalyst loadings, easy handling due to its non-toxicity, cheap price and low-toxic reaction waste.[7] In addition, the cyanations of aryl and arylvinyl bromides under dielectric heating in ionic liquids or under ligand-free conditions were recently described.[8] Among several electron rich heterocyclic systems, phenothiazines are particularly important for pharmaceutical applications.[9,10] Phenothiazines are also able to cleave DNA upon photochemical induction.[11] As a consequence of low oxidation potentials, these readily form stable radical cations and their physiological activities can be attributed to this circumstance.[12] The reversibility of the first oxidations[9,13] giving rise to characteristic, deep colored radical cation absorptions, make them excellent spectroscopic probes in molecular and supramolecular arrangements for photoinduced electron transfer (PET) studies[14] and as materials for scientific motifs.[15] As part of our program directed toward phenothiazinyl based functional organic molecules,[16,17] we became interested in cyanophenothiazines as building blocks for synthetic and electronic purposes. Cyanophenothiazines are usually prepared either by de novo synthesis of the phenothiazinyl core or by elimination from amides or oximes.[18] Catalytic reactions have not been reported so far. Herein, we communicate the first synthesis and electronic properties of cyano(oligo)phenothiazines, in particular, electrochemical behavior and photoluminescence properties.

Due to their rich transformation potential and with regard to grafting and fine-tuning electronic properties

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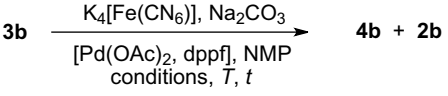
doi:10.1016/j.tetlet.2008.03.071

we now have focused on cyano(oligo)phenothiazines. The transposition of the Pd-catalyzed cyanation of 3-bromo and 3,7-dibromo (oligo)phenothiazines, **1** and **3**,[17] according to Beller's standard protocol[7] furnished 3-cyano(oligo)-phenothiazines **2a** and **2c**, and 3,7-dicyano-(oligo)phenothiazines **4a** and **4c** in moderate to excellent yields by conductive or dielectric heating (Fig. 1).[19,20]

Most interestingly, the diphenothiazinyl bromide **1b** and dibromide **3b** react in Beller cyanations at 160 °C or at 120 °C under conductive heating only partially in the expected fashion. The 3-cyano dyad **2b** was only obtained in 30% yield along with the unsubstituted quaterphenothiazine **5**[17] in 15% yield, whereas the 3,7-dicyano dyad **4b** was obtained in 35% yield along with the monocyanation product **2c** in 24% yield (Fig. 2).

The structures of the (oligo)phenothiazinyl nitriles **2** and **4** are unambiguously supported by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry and correct combustion analysis. Although, Beller cyanation works reliably with bromides **1a**, **1c**, **3a**, and **3c**, the biphenothiazine derivatives **1b** and **3b** deviate in chemo-selectivity. The unexpected reductive homocoupling of **1b** to tetrad **5** and the reductive debromination of **3b** to the monocyano derivative **2b** clearly indicate that the diphenothiazinyl unit has peculiar electronic properties. The combination of potassium hexacyanoferrate as the only suitable reductant and electron transfer processes in the coordination sphere of Pd might rationalize the formation of unusual by-products in significant amounts. This also prompted us to attempt an optimization of the dicyanation of **3b** to give **4b** under conventional and microwave heating (Eq. 1, Table 1).

Table 1
Optimization studies of the dicyanation of **3b** under conductive and dielectric heating[a]



(1)

Entry	Heating method	T (°C)	t (h)	Yields of **4b** and **2b**[b] (%)
1	Oil bath	120	16	35 (**4b**) + 24 (**2b**)
2	Oil bath	150	48	39 (**4b**) + 15 (**2b**)
3	Oil bath	160	1	<1 (**4b**) + <1 (**2b**)
4	Microwave oven	120	0.5	25 (**4b**) + 6 (**2b**)
5	Microwave oven	140	0.33	42 (**4b**) + 42 (**2b**)
6	Microwave oven	160	1	34 (**4b**) + 11 (**2b**)
7	Microwave oven	180	0.5	34 (**4b**) + 9 (**2b**)
8[c]	Microwave oven	160	1	0 (**4b**) + 0 (**2b**)

[a] General conditions: 1 equiv of **3b**, 0.5 equiv of dry $K_4[Fe(CN)_6]$, 2 equiv of dry Na_2CO_3, 0.2 mol % of $Pd(OAc)_2$, 0.4 mol % of dppf, dry NMP.
[b] Isolated yields after column chromatography.
[c] Without palladium/dppf as a catalyst.

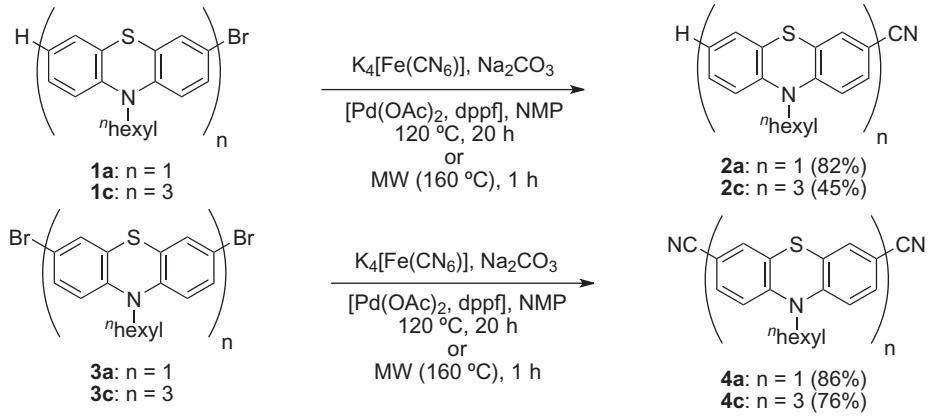


Fig. 1. Synthesis of 3-cyano(oligo)phenothiazines **2a** and **2c**, and 3,7-dicyano(oligo)phenothiazines **4a** and **4c**.

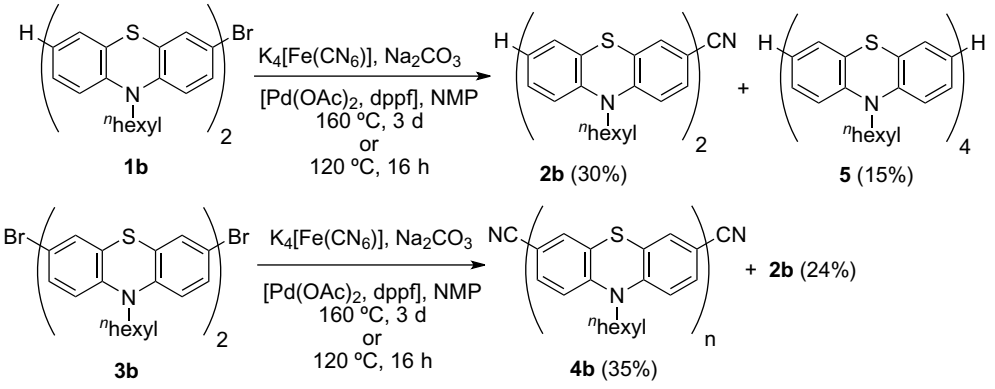


Fig. 2. Synthesis of cyanated diphenothiazines **2b** and **4b**.

Table 2
Selected electronic properties of cyano (oligo)phenothiazines **2** and **4** (absorption and emission spectra[a] and cyclic voltammetry[b] recorded in CH_2Cl_2, $T = 298$ K)

	Absorption $\lambda_{max,abs}$ (nm)	Emission $\lambda_{max,em}$ (nm)	Quantum yield (%)	$E_0^{0/+1}$ (mV)	$E_0^{+1/+2}$ (mV)	$E_0^{+2/+3}$ (mV)
2a	268, 340	474, 491 (sh)	11	952	—	—
2b	279, 324, 375	481, 507 (sh)	25	711	1040	—
2c	282, 328, 376	474, 491 (sh)	27	631	781	1012
4a	277, 335, 366	479, 507 (sh)	19	1179	—	—
4b	281, 333, 376	481, 510 (sh)	18	936	1098	—
4c	281, 333, 377	474, 491 (sh)	22	656	981	1030

[a] Determined in CH_2Cl_2 at $c = 10^{-7}$ M with coumarine 1 as a standard ($\Phi_f = 0.73$).
[b] $v = 100$ mV/s, electrolyte: $^nBu_4N^+PF_6^-$, Pt working electrode, Pt counter electrode, Ag/AgCl reference electrode.

Prolonged heating at higher temperature, either conventional or in the microwave oven, proves to be less favorable (entries 2, 6, and 7 vs entries 1 and 5). In comparison to conductive heating reactions under dielectric heating are not only significantly faster but also higher yielding (entries 3 and 6). The absence of the Pd catalyst precursor and the dppf ligand (entry 8) does not lead to any product formation indicating that the oxidative addition of the phenothiazinyl bromides clearly is a Pd-mediated elementary step that cannot be accomplished by potassium hexacyanoferrate alone.

The electronic properties of the (oligo)phenthiazinyl nitriles **2** and **4** were investigated by absorption and emission spectroscopy and cyclic voltammetry (Table 2). Furthermore, the quantum yields were determined with coumarine 1 as a standard.

All the compounds display intense blue to greenish-blue daylight fluorescence with fluorescence quantum yields between 11% and 27% and remarkable Stokes-shifts (5800–8300 cm^{-1}). These substantial Stokes-shifts can be attributed to significant geometrical changes upon excitation from a highly non-planar ground-state to a largely planarized excited state.[21] According to absorption and emission spectra, the effective conjugation length is already reached with two conjugatively linked phenothiazinyl units. In particular, the emission data can be attributed to the presence of a 3-cyano phenothiazinyl moiety which seems to be the dominant fluorophore. The cyclic voltammograms of all the cyano phenothiazines clearly show reversible oxidation potentials reflecting the number of conjugatively linked phenothiazinyl units. As a consequence of the strong electron-withdrawing nature of the nitrile group, the oxidation potentials of **2** are anodically shifted to a significant extent. Dicyano (oligo)phenothiazines **4** are even harder to oxidize and for monophenothiazines **2a** and **4a** the first oxidation potentials differ by more than 220 mV.

In summary, we have transposed the Beller cyanation to electron rich phenothiazines, predominantly under dielectric heating, giving rise to the formation of (oligo)phenothiazinyl nitriles **2** and dinitriles **4**. The electronic properties, as determined by absorption and emission spectroscopy and cyclic voltammetry, reveal a class of highly fluorescent extended π-electron systems with large Stokes-shifts (5800–8300 cm^{-1}) and substantial quantum yields (11–27%). Furthermore, these fluorophores are reversibly oxidized at potentials that correlate with number of the phenothiazinyl units. Cyano phenothiazines not only are suitable electroactive building blocks for heterocycle synthesis but also are versatile π-systems as the ligands for complexation with transition metals or for further transformation well suited for the ligation of electrophores to surfaces and into mesoporous materials. Studies directed toward these applications and to the elucidation of the electronic structure by computational and photophysical methods are currently underway.

Acknowledgments

The support of this work by the Deutsche Forschungsgemeinschaft DFG (Priority program 1181), the Deutscher Akademischer Austauschdienst DAAD (scholarship for L.N.P.), and by the Fonds der Chemischen Industrie is gratefully acknowledged. The authors also thank the BASF AG for the generous donation of chemicals.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.071.

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19. *General procedure for cyanations under dielectric heating*: Anhydrous Na_2CO_3 (1 equiv per C–Br bond), $K_4[Fe(CN)_6$ (0.25 equiv per C–Br bond) (ground to a fine powder and dried in vacuum), $Pd(OAc_2)$ (0.001 equiv per C–Br bond) and dppf (0.002 equiv per C–Br bond) were placed in a 5 mL microwave tube. Then, the phenothiazinyl bromide **1** or dibromide **3** (1 equiv) and 3 mL of dry NMP were added. The tube was sealed, placed in the microwave cavity, and the reaction mixture was stirred under irradiation. After cooling to room temperature 150 mL of dichloromethane, 20 mL of saturated Na_2SO_3 solution and 100 mL of deionized water were added to the reaction mixture. The organic phase was separated and washed once with the same amount of water. After drying with anhydrous magnesium sulfate, the solvents were evaporated and the residue was purified by flash chromatography on silica gel (hexane/diethylether 60:1) to furnish the cyano phenothiazines **2** or **4** as yellow solids, resins, or oils. *Compound* **2a**: Yield: 3.55 g (82%), yellow oil. R_f (hexane/acetone 5:1): 0.55. ^{1}H NMR (CD_2Cl_2, 500 MHz): $\delta = 0.87$ (t, $J = 7.3$ Hz, 3H), 1.30 (m, 4H), 1.42 (m, 2H), 1.77 (m, 2H), 3.85 (t, $J = 7.3$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 1H), 6.90 (m, 1H), 6.97 (dt, $^dJ = 1.5$ Hz, $^tJ = 7.3$ Hz, 1H), 7.10 (dd, $J = 7.3$ Hz, $J = 1.5$ Hz, 1H), 7.19 (m, 1H), 7.37 (m, 1H), 7.41 (dd, $J = 1.5$ Hz, $J = 8.5$ Hz, 1H). ^{13}C NMR (CD_2Cl_2, 125 MHz) $\delta = 13.4$ (CH_3), 22.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 31.0 (CH_2), 47.4 (CH_2), 104.7 ($C_{quat.}$), 114.8 (CH), 115.7 (CH), 118.4 ($C_{quat.}$), 123.0 ($C_{quat.}$), 123.2 (CH), 125.2 ($C_{quat.}$), 127.1 (CH), 127.4 (CH), 129.9 (CH), 131.3 (CH), 143.3 ($C_{quat.}$), 148.9 ($C_{quat.}$). UV/vis (CH_2Cl_2): λ_{max} (ε) = 268 nm (29535), 340 nm (4580). IR (KBr): $\tilde{\nu} = 3061$, 2927, 2855, 2222, 1599, 1574, 1494, 1461, 1401, 1364, 1336, 1283, 1251, 1197, 1136, 1104, 1041, 884, 817, 749, 617, 586, 522 cm^{-1}. MS (EI$^+$) *m*/*z* (%): 308.0 (100, M^+), 236.9 (88, $M^+-C_5H_{11}$), 223.0 (75, $M^+-C_6H_{13}$), 205.0. Anal. Calcd for $C_{19}H_{20}N_2S$ (308.5): C, 73.99; H, 6.54; N, 9.08. Found: C, 74.15; H, 6.49; N, 8.90. *Compound* **4c**: Yield: 0.40 g (76%), yellow resin. Mp 117 °C. R_f (hexane/acetone 5:1): 0.19. ^{1}H NMR (CD_2Cl_2, 500 MHz): $\delta = 0.88$ (m, 9H), 1.30–1.41 (m, 12H), 1.43 (m, 6H), 1.77 (m, 6H), 3.83 (m, 6H), 6.82–6.90 (m, 5H), 7.18 (m, 2H), 7.29 (m, 2H), 7.29–7.34 (m, 7H), 7.39 (m, 2H). ^{13}C NMR (CD_2Cl_2, 125 MHz): $\delta = 13.4$ (CH_3), 22.4 (CH_2), 26.1 (CH_2), 31.0 (CH_2), 47.5 (CH_2), 104.7 ($C_{quat.}$), 114.7 (CH), 115.2 (CH), 115.9 (CH), 118.4 ($C_{quat.}$), 123.3 ($C_{quat.}$), 124.5 (CH), 124.6 (CH), 124.9 (CH), 125.1 (CH), 127.8 (CH), 128.6 (CH), 129.8 (CH), 131.4 (CH), 133.2 ($C_{quat.}$), 134.9 ($C_{quat.}$), 142.0 ($C_{quat.}$), 143.8 ($C_{quat.}$), 148.6 ($C_{quat.}$). IR (KBr) $\nu = 2927$, 2855, 2222, 1604, 1581, 1459, 1416, 1378, 1335, 1244, 1197, 1105, 876, 807, 732, 587 cm^{-1}. UV/vis: λ_{max} (ε) = 281 nm (106400), 328 nm (26700), 377 nm (27500). MS (MALDI) *m*/*z*: calcd for $C_{56}H_{57}N_5S_3$: 895.378; found: 895.340 (M^+).
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