Preparation of Non-Symmetrical 2,3-Bis-(2,2'-oligopyridyl)pyrazines via 1,2-Disubstituted Ethanones

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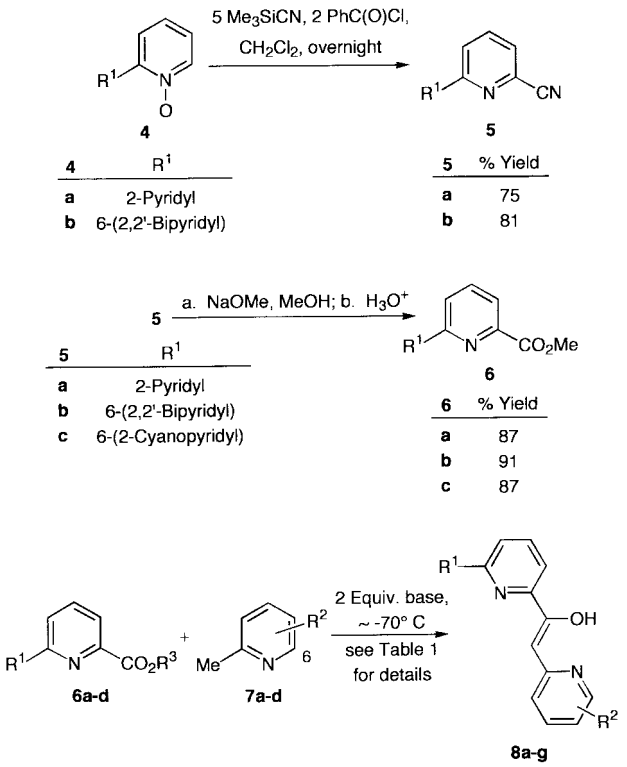
Abstract: Sequential oxidation of the condensation products between alkyl 2,2'-oligopyridyl carboxylates and 6-methyl pyridine homologues with *m*-CPBA, then iodine affords the corresponding mixed α-diketones. These compounds are readily transformed into the respective mixed bis-oligopyridyl pyrazines, a class of compounds of interest for supramolecular chemistry.

Key words: pyrazine, pyridine, C-C coupling, enol, oxidation

The supramolecular chemistry of substances incorporating the pyrazine ring is limited to a handful of oligoheterocyclic compounds.[1,2] The arrangement of that ring's donor atoms and π-electron system, as well as the presence of π-stacking effects orthogonal to the ring plane,[3] make compounds which contain it and their metallosupramolecular complexes attractive candidates for electronic delocalization studies. We are interested in the preparation, characterization and supramolecular chemistry of oligo-2,2'-pyridyloligopyrazines having the general formula **1**.[4-6] The 2,3-disubstitution pattern about the pyrazine ring dictates that the steric interaction of appended groups will also contribute to their topology and supramolecular chemistry. In view of this multi-faceted behaviour, the under-representation of such compounds from the literature is possibly due to the paucity of methods for their preparation.

Simpler substances serving as both model substances and eminent retrosynthetic candidates are 2,3-bis(2,2'-oligopyridyl)pyrazines **2**, bearing dislike oligopyridyl substituents. In analogy to our earlier synthesis of some symmetrical oligopyridyl pyrazines,[5] we reasoned that access to the non-symmetrical compounds could be gained through the corresponding α-diketones **3**. We have already described a simple preparation of one such compound based on the mixed benzoin condensation of appropriate aldehydes.[4] However, the anticipated chromatographic separation of larger bis-oligopyridyl precursors constitutes a drawback to this method's extension to larger homologues. Thus, we sought a preparatory method by which two arbitrary oligopyridyl fragments are coupled to afford a crude reaction mixture containing a single bis-oligopyridyl product and in which the aforementioned junction can later be transformed into a pyrazine ring.

Our approach used the Claisen-type condensation of oligopyridyl-6-carboxylate esters with appropriate active hydrogen compounds. The ester starting materials were prepared by treatment of the oligopyridyl-N-oxides **4a–b**[7] with excess trimethylsilyl cyanide and benzoyl chloride according to Fife's procedure[8] to afford nitriles **5a–b** (Scheme 1).[9] Basic methanolysis of **5a–c**,[10] followed by acidic hydrolysis of the intermediate methyl imidates gave esters **6a–c** in good overall yields.[11] This simple procedure is superior to the known preparations of related nitriles and related esters in terms of yields and number of synthetic steps.[12]



Scheme 1 Preparation of Tautomeric 1,2-Bis(2,2'-oligopirydyl)ethanones **8**

Slow addition of the esters **6a–d** to solutions of the 6-methyl oligopyridine derivatives **7a–d** and 2 equivalents of base in Et_2O or 1,2-dimethoxyethane (DME) at low temperature furnished the keto-enol tautomeric condensation products **8a–g** after work-up and column chromatography (Scheme 1 and Table 1). The use of sterically hindered lithium tetramethylpiperidide (LTMP) instead of lithium diisopropylamide (LDA) was in some cases necessary to prevent reaction of the base with the esters. Products containing unsubstituted oligopyridyl ring systems (*e.g.*, **8a–**

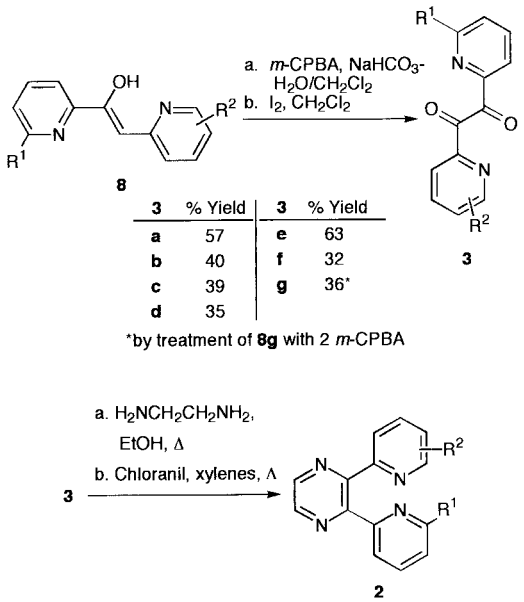
Table 1 Condensation of Esters **6a-d** with 6-Methylpyridine Derivatives **7a-d** Affording Ethanones **8**

8	R^1	R^2	R^3	Reaction conditions	% Yield of 8
a	2-Pyridyl	H	Me	A[a]	46
b	6-(2,2'-Bipyridyl)	H	Me	A[a]	78
c	6-(2-Methoxycarbonylpyridyl)	H	Me	2 × A[a]	92
d	6-(2,2'-Bipyridyl)	2-Pyridyl	Me	B[b]	28
e	2-Pyridyl	2-(5-Methylpyridyl)	Me	C[c]	39
f	2-Pyridyl	2-(6-Methylpyridyl)	Me	D[d]	71
g	H	2-(6-Methylpyridyl)	Et	A[a]	40

[a]: 2 equiv. LDA, Et_2O; [b]: 2 equiv. LTMP, DME; [c]: 1 equiv. ^{n}BuLi + 1 equiv. LTMP, Et_2O; [d]: 1 equiv. ^{n}BuLi + 1 equiv. LTMP, DME.

d) could be recrystallized and characterized as pure, crystalline materials.[13] Hot solutions of those chromatographically pure derivatives containing methyl substituents (**8e–g**) invariably precipitated poorly-soluble dark-red coloured films, which according to ^{1}H NMR spectroscopic analysis, consisted of polymeric materials. In the case of **8f**, no crystalline material could be isolated. Thus, these three compounds were employed without further purification in the following reaction step.

The oxidation of **8** to the α-diketones **3** was the key step to this synthetic pathway. Here, we sought an alternative reaction sequence to the classical selenium dioxide method[14] which would provide the products in more reliable yields. This was possible by treatment of **8** with 1 equivalent of *m*-CPBA in a mixture of dichloromethane and aqueous sodium bicarbonate solution, giving the non-symmetrical 1,2-dihydroxyolefins (not shown) already containing various amounts of **3**. Complete oxidation of this material was achieved using a solution of 1 equivalent of iodine per dihydroxyolefin, and afforded clean **3** after work-up and column chromatography (Scheme 2).[15]



Scheme 2 Synthesis of Pyrazine Target Molecules **2**

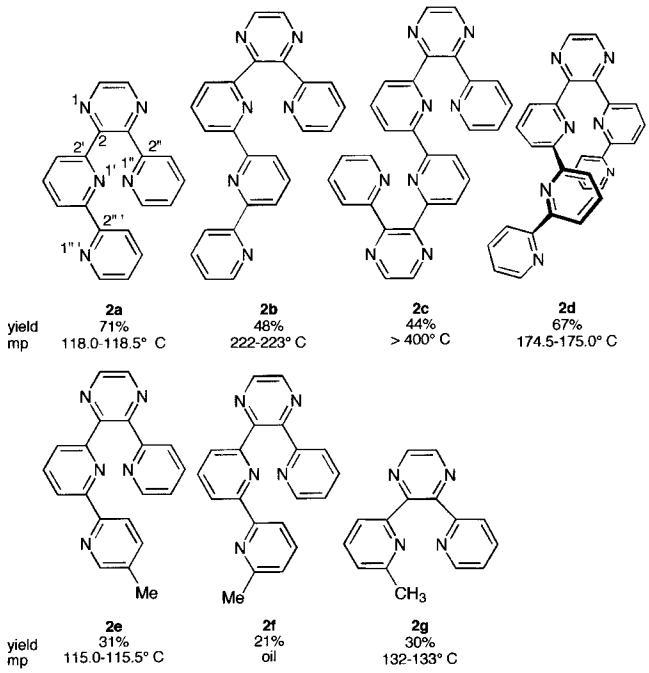
The preference of **8** for a novel reactivity mode analogous to the Rubottom oxidation of silyl enol ethers,[16] as opposed to that in the Baeyer-Villiger reaction,[17] is illustrated by the absence of ester side products from the crude dihydroxyolefin reaction mixtures according to ^{1}H NMR spectroscopic analysis. Other oxidizing reagents gave only poorly characterizable mixtures.[18] The position of the tautomeric equilibria in **8** did not exert any clear influence on the isolated yields of **3**. Except for compound **3e**, all α-diketones were obtained as pure, crystalline solids. Although **3f** could be recrystallized following column chromatography, significant material loss due to partial decomposition on silica gel resulted in its being employed in a synthetically pure state for the next reaction step.

Condensation of **3a–g** with 1,2-diaminoethane, followed by chloranil oxidation in xylene under reflux afforded the pyrazine derivatives **2a–g** after column chromatography on deactivated alumina/CH_2Cl_2 - EtOAc and/or silica gel/Et_2HN - hexanes (Scheme 2).[19] The variation in isolated yields (Table 2) for these compounds partially reflects the instability of some precursors (**8e–g**) and the low solubility of a few of the products (*e.g.*, **2b–c**; solubility of **2c**: less than 1 mg/mL). However, all pyrazine derivatives **2** were stable materials whose identity and purity was attested to by either satisfactory analytical data or the combination of clean spectra and high resolution mass spectroscopy.

Some properties of compounds **2a–g** deserve preliminary comment. Inspection of molecular models shows that the minimization of dipole-dipole interactions within the separate oligopyridyl chains,[20] as well as steric effects both within and between them, would result in a *double*-helical twisting of the oligopyridyl units about one another. Proof of this is seen in the ^{1}H NMR spectrum of *e.g.*, bipyridyl pyridyl **2a** (see Ref.[19]). On the terminal pyridyl substituent in the bipyridyl fragment, H-3"' absorbs at an abnormally high field position. NOE effects observed between H-3"' and H-3"/H-6" of the solitary pyridine ring leads us to ascribe this to edge-on-surface shielding effects between the two terminal pyridine rings.[21]

This phenomenon, the origins of the comparatively low solubility and high melting point of symmetrical derivative **2c**, and the scope and limitations of this reaction sequence will be addressed in upcoming papers.

Table 2 Bis(oligopyridiyl)pyrazines **2** Synthesized



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(9) **5a**: To an ice-cooled solution of **4a** (8.41 g, 48.9 mmol) and trimethylsilyl cyanide (31 mL, 240 mmol) in ca. 130 mL dry CH_2Cl_2 under N_2 was carefully added benzoyl chloride (11 mL, 98 mmol). After stirring overnight at r.t., 10% aq Na_2CO_3 was carefully added to the chilled reaction mixture and it was concentrated at 200 mbar to complete crude product precipitation. This was collected by filtration, washed with water, dried in vacuum over P_4O_{10} and repeatedly recrystallized from hexane to give **5a** (6.71 g) as fluffy colourless needles, mp 132-133° C (Lit.:[12b] 130-131° C); **5b**: see procedure for **5a**. Purification by column chromatography (15:85 - EtOAc:CH_2Cl_2, silica gel) and recrystallization (heptane-CH_2Cl_2), mp 152-153° C; *Anal.* Calcd for $C_{16}H_{10}N_4$: C, 74.41; H, 3.90; N, 21.69. Found: C, 73.82; H, 4.10; N, 21.00.

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(11) *Typical procedure:* **6a**: A solution of **5a** (5.71 g, 31.5 mmol) and sodium methoxide (55 mmol) in dry MeOH (100 mL) was stirred overnight under N_2 at r. t. Then, AcOH (3.2 mL, 55 mmol) and solid $NaHCO_3$ were added, and solvent removed in vacuo. The remaining material was dissolved in EtOAc/sat. aq. $NaHCO_3$ (80/20 mL), the phases separated, the aq layer extracted with EtOAc and the combined organic extracts washed with sat. aq $NaHCO_3$, water and brine. After drying ($MgSO_4$) and solvent removal in vacuo, the resulting oily methyl imidate ester was stirred in MeOH (50 mL) and water (50 mL), acidified to ca. pH 1 with 5% aq. H_2SO_4, at r t. (2 h). Then, the chilled mixture was brought to pH 9 with 2 M aq. NaOH, EtOAc (80 mL) added, and after brief agitation, the phases separated. The aq. layer was extracted with EtOAc, the combined organic solutions washed with water and brine, dried ($MgSO_4$) and concentrated under vacuum to give a pale yellow solid. Hot filtration and repeated recrystallization (hexanes) afforded **6a** (5.85 g) as colourless crystals, mp 82-83° C; *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.23; H, 4.88; N, 12.88.

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(13) *Typical procedure:* **8a**: a solution of **7a** (0.43 g, 4.7 mmol) in dry Et_2O (9 mL) was added to LDA (9.8 mmol) in Et_2O (40 mL) at -70 to -65° C under N_2. After ca. 30 min at -65° C, **6a** (1.0 g, 4.7 mmol) in Et_2O (15 mL) was added dropwise to the yellow solution. The stirred mixture was warmed to 25° C (4 h), sat. aq NH_4Cl (50 mL), then EtOAc (50 mL) added. The phases were separated, the aqueous phase extracted with EtOAc, the combined organic extracts washed with water, dried ($MgSO_4$) and solvent removed in vacuo. Column chromatography (7:93 - EtOAc:CH_2Cl_2, alumina activity III) of the resulting red oil and recrystallization (MeOH), afforded **8a** (0.58 g) as yellow needles, mp 115-116° C; *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.42; H, 5.26; N, 14.52.

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(15) *Typical procedure:* **3a**: a solution of **8a** (0.70 g, 2.6 mmol) in CH_2Cl_2 (25 mL) and 0.5 M aq. $NaHCO_3$ (7 mL) was treated with *m*-CPBA (85%, 0.52 g, 2.6 mmol) over 20 min. After stirring overnight, the mixture was extracted with sat. aq. $NaHCO_3$ and H_2O dried (Na_2SO_4) and the solvent removed in vacuo to leave an orange solid (0.68 g). A suspension of this material in dry CH_2Cl_2 (20 mL) was then added to a solution of I_2 (0.46 g, 1.8 mmol) in CH_2Cl_2 (50 mL) and stirred at r.t. (2.5 h). A brown oil precipitated during this time. Sat. aq

$NaHCO_3$ was then added, and the mixture was vigorously stirred and decanted. The residual oil was dissolved in CH_2Cl_2/sat. aq $NaHCO_3$ in an ultrasonic cleaning bath. The combined organic extracts were washed with water, dried (Na_2SO_4) and solvent removed in vacuo. Column chromatography (30:70 - EtOAc:CH_2Cl_2 on silica gel) afforded **3a** (0.42 g) as a crystalline mass, recrystallized (abs. EtOH) for elemental analysis, mp 129.5-130° C; EI-MS (70 eV): m/z (relative intensity) = 289 (M^+, 45), 261 (48), 233 (54), 155 (100); *Anal.* Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.30; H, 3.86; N, 14.43.

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(19) *Typical procedure:* **2a:** A solution of **3a** (0.42 g, 1.4 mmol) and 1,2-diaminoethane (0.097 mL, 1.4 mmol) in EtOH (10 mL) was heated under reflux (2 h). After solvent evaporation in vacuo, the residual red solid and chloranil (0.36 g, 1.4 mmol) in xylene (10 mL) were heated under reflux (6 h). The cooled reaction mixture was filtered through a celite pad, the residual insoluble material treated with PhMe and then 2 M aq. NaOH in an ultrasonic cleaning bath with repeated filtering of the supernatant solution (3 x 10 mL, each). The combined organic phases were washed with 2 M aq NaOH, then water and extracted into 3 M aq HCl. The combined aqueous extracts were washed with Et_2O, rendered basic by addition of ice-cold 2 M aq. NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried (Na_2SO_4), concentrated in vacuo and the resulting viscous oil purified by column chromatography (3:97 - EtOAc:CH_2Cl_2, alumina activity III) to afford **2a** (0.32 g) as a pale yellow crystalline solid, recrystallized (CH_2Cl_2 - heptane) for elemental analysis; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (s, 2H, H-5; H-6), 8.58 (br d, J = 4 Hz, 1H, H-6'''), 8.42 (dt, J = 1.3; 4.7 Hz, 1H, H-6''), 8.36 (dd, J = 1.0; 7.9 Hz, 1H, H-5'), 8.12 (dd, J = 1.0; 7.7 Hz, 1H, H-3'), 7.96 (t, J = 7.8 Hz, 1H, H-4'), 7.79-7.82 (m, 2H, H-3'', H-4''), 7.52 (dt, J = 7.8; 1.7 Hz, 1H, H-4'''), 7.22 (br d, J = 6.8 Hz, 1H, H-3'''), 7.17-7.21 (m, 2H, H-5''; H-5'''); EI-MS (70 eV): m/z (relative intensity) = 311 (M^+, 70), 310 (100), 283 (7), 233 (20), 155 (8); *Anal.* Calcd for $C_{19}H_{13}N_5$: C, 73.30; H, 4.21; N, 22.49. Found: C, 73.17; H, 4.36; N, 22.84.

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