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Toward benign syntheses of pyridines involving sequential solvent free aldol and Michael addition reactions

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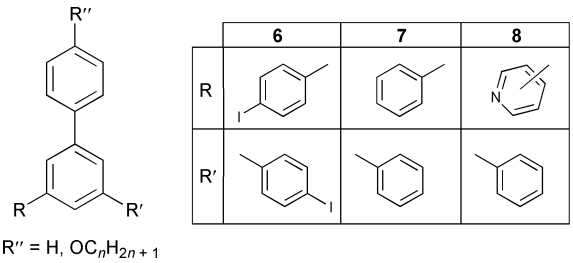
Kröhnke type pyridines are readily accessible *via* a sequential solventless aldol condensation and Michael addition involving solid NaOH, followed by treatment with ammonium acetate in acetic acid, as a one pot reaction, which enables both symmetrical and unsymmetrical 2,6-bisaryl substituted pyridines to be isolated in high yield, typically > 75%.

Kröhnke type pyridines[1] and other substituted pyridines including the related terpyridines[2-4] are prominent building blocks in supramolecular chemistry with their π-stacking ability, and directional H-bonding and coordination. In general, conventional methods used in the synthesis of substituted pyridines use volatile organic solvents and display only moderate to low yields.[2,5,6] In developing a more versatile route to such compounds, where possible adopting the principles of 'Green Chemistry',[7] we have established that using solventless conditions involving sequential aldol and Michael addition reactions results in a dramatic improvement in yield, and indeed allows access to a range of compounds not accessible using conventional methods involving organic solvents. Overall, this versatile new approach can be applied to the synthesis of a range of symmetrical and unsymmetrical terpyridines, and pyridines in general bearing aryl groups in the 2, 4 and 6 positions.

The significance of our findings also relates to reducing the use of organic solvents as potentially toxic and hazardous materials,[7] as well as its simplicity and mild conditions, and inherent lower costs, with more likely industrial applications. Moreover, the findings are further credence to challenge the conventional view of using organic solvents in synthesis even in the absence of reasons to do so.[8] The use of solventless reactions is gaining prominence with recent advances in solventless reactions under mild conditions including the aldol condensation,[8–12] and others recently reviewed by Tanaka and Toda.[8]

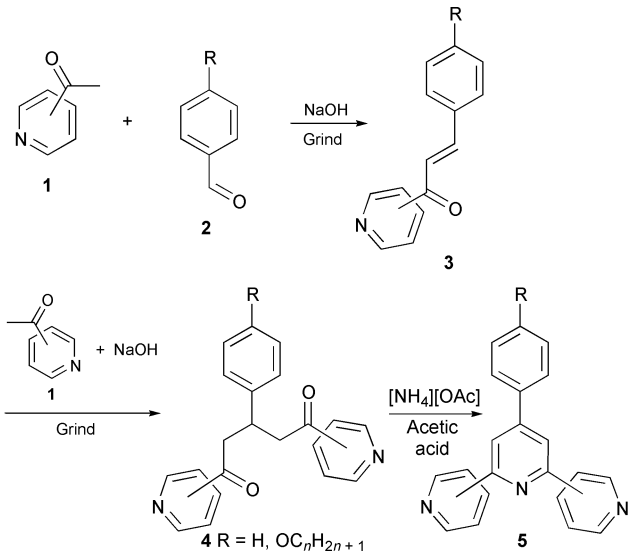
Synthetic details are summarised in Scheme 1.† In a typical experiment, the benzaldehyde **1** and acetylpyridine **2** analogues were mixed together as liquids with a pestle and mortar in the presence of NaOH. Over a period of *ca*. 10 min constant aggregating, the reaction solidified as the aldol condensation product **3**. For the same reaction using two equiv. of the acetylpyridine **2**, the initial product **3** underwent a Michael addition to form the diketone **4**. The addition of a second acetylpyridine **1** to the condensation product **3** provided a direct route to unsymmetrical diketones. The facile formation of **3** and **4** is essentially quantitative and subsequently does not require isolation from the reaction mixture before the tertiary step whereby the diketone **4** was consequently treated with ammonium acetate in acetic acid to generate the terpyridyl product **5** in high yield, > 75%. The structure of the 4,4″ isomer of **5**, R = OC_8H_{17}, *viz*. 4′-(4-octyloxyphenyl)-4,2′:6′,4″-terpyridine, Fig. 1, has been determined from X-ray diffraction data‡ as a representative of compounds prepared thus far using this new synthetic strategy.

The new method herein has also been applied to a number of analogues including the formation of a series of 2,6-bis(4-iodophenyl)-4-phenylpyridines (**6**), 2,4,6-triphenylpyridines (**7**) and bipyridines (**8**).



A synthetic route to a diketone similar (pyridine nitrogens in the 2′ position, R = ^{t}Bu) to the intermediate **4** was reported to yield the Michael addition product, *ca*. 40% yield, by reacting two equiv. of 2-acetylpyridine with the *para*-substituted benzaldehye in the presence of NaOH, in EtOH.[13] All of our corresponding reactions, conducted using the solventless conditions described above, were determined to be essentially quantitative by ^{1}H and ^{13}C NMR techniques. This therefore allows the intermediate **4** to be reacted on to form the product **5** and thus dispense with extensive recrystallisation and/or chromatographic purification steps. It is noteworthy that when these solvent based methods are adopted in an attempt to prepare 4′-(4-alkoxyphenyl)-4,2′:6′,4″-terpyridines, only the cyclohexyl product **9** is isolated from the complex reaction mixture which is devoid of target molecules. Compound **9**, which was characterised using NMR data, R = OC_4H_9, and X-ray diffraction data, R = H, does however incorporate the expected intermediate **4**.[14]

Typically unsymmetrical Kröhnke type pyridines have been synthesised by reacting the aldol product **3** with a *N*-[1-oxo-



Scheme 1

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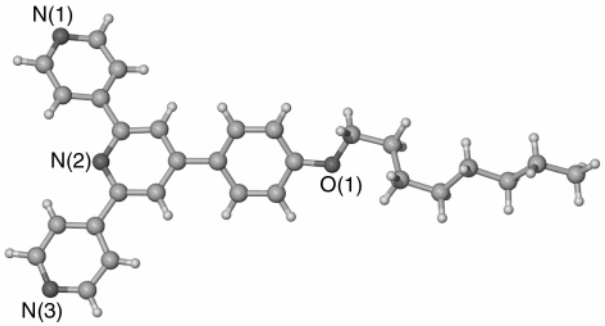
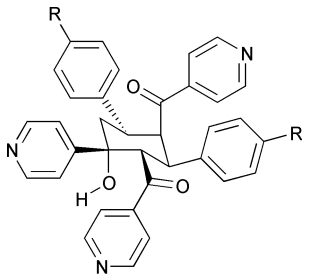


Fig. 1 Molecular structure of 4′-(4-octyloxyphenyl)-4,2′: 6′,4″-terpyridine.



9 R = H, OC_nH_{2n+1}

(2-aryl)ethyl]pyridinium iodide or bromide and ammonium acetate.[2,3] These reactions seldom afford the products in more than a 45% yield, and this coupled with the fact that the pyridinium halide often has to be synthesised can lead to an expensive, time consuming protocol. The versatility of the solventless reactions is demonstrated by the facile inexpensive formation of such unsymmetrical Kröhnke type pyridines as **5** and **8** in high yield.

The above solventless reactions involve the reaction of liquids formed by mixing two organic compounds, at most only one of them being a solid, with the solid intermediate (**3**) reacted with a liquid. At no time was there a reaction of a solid with a solid, athough this is possible given our previous endeavours with solventless aldol condensation involving two organic solids which show that the primary process is the formation of a eutectic mixture with a melting point below rt. This mixture then reacts with the solid NaOH *en route* to the product, rather than two solids reacting through crystal deformation mechanisms.[8,15]

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Notes and references

† *Synthesis*: *e.g.* 4′-(4-butyloxyphenyl)-4,2′:6′,4″-terpyridine, **5**: 4-acetylpyridine (3.02 g, 24.9 mmol) and freshly distilled 4-butyloxybenzaldehyde (2.22 g, 12.5 mmol) and NaOH pellets (1.00 g, 25.0 mmol) were crushed together with a pestle and mortar until a pale yellow powder was formed (*ca*. 15 min). [Diketone **5**: MS (ESI+) for $C_{25}H_{26}N_2O_3$ ([*M* + Na]$^+$): calcd: 425.48; found: 425.3. FT-IR: $\nu_{(C=O)}$ 1695 cm^{-1} KBr]. The powder was added to a stirred solution of ammonium acetate (5.00 g, excess) in glacial acetic acid (300 cm^3). The reaction was heated at reflux (2 h), affording a dark green solution. The reaction mixture was neutralised with saturated potassium carbonate, extracted with $CHCl_3$ (3 × 100 cm^3) and dried (magnesium sulfate). All volatiles were removed under *vacuo* yielding a viscous dark green oil. The white product was recrystallised from MeOH. Yield: 3.63 g (76%, 9.53 mmol). Mp 185.2 °C. Anal. found (expected): C 78.58 (78.71), H 5.96 (6.08), N 10.86 (11.02)%. MS (EI+, 70 eV, 200 °C) for $C_{25}H_{23}N_3O$ ([M]$^+$): calcd: 381.47; found: 381.^{1}H NMR (300 MHz, $CDCl_3$, 300.0 K): δ = 8.76 (AA'XX', 4H, pyridine *ortho* to N), 8.04 (AA'XX', 4H, pyridine *meta* to N, *ortho* to trisubstituted pyridine), 7.96 (s, 2H, pyridine *ortho* to phenyl), 7.58 (AA'XX', 2H, phenyl *meta* to OC_4H_9 chain), 7.04 (AA'XX', 2H, phenyl *ortho* to OC_4H_9 chain), 4.04 (t, J = 6.5 Hz, 2H, OCH_2), 1.81 (m, 2H, OCH_2CH_2), 1.52 (m, 2H, CH_2CH_3), 0.99 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300.0 K): δ = 159.62, 154.12, 149.64, 149.42, 145.23, 128.77, 127.29, 120.22, 117.32, 114.32, 66.97, 30.24, 18.23, 12.82. 2,6-bis(4-iodophenyl)-4-phenylpyridines, **6**: the reaction proceeded as above *via* the addition of 4′-iodoacetophenone (3.00 g, 12.2 mmol) and 4-octyloxybenzaldehyde (1.43 g, 6.09 mmol) in the absence of light. The product (**7**) separated as a colourless oil from the acetic acid solution, the analytically pure product solidified on further cooling. Yield: 3.45 g (85%, 5.20 mmol). Mp 120 °C. Anal. found (expected): C 54.08 (54.17), H 4.67 (4.55), N 1.96 (2.04)%. MS (EI+, 50 eV, 200 °C) for $C_{31}H_{31}I_2NO$ ([M]$^+$): calcd: 687.39; found: 688.0. ^{1}H NMR (300 MHz, $CDCl_3$, 300.0 K): δ = 7.89 (AA'XX', 4H, *meta* to I), 7.82 (AA'XX', 4H, *ortho* to I), 7.79 (s, 2H, pyridine), 7.64 (AA'XX', 2H, phenyl *meta* to OC_8H_{17} chain), 7.02 (AA'XX', 2H, phenyl *ortho* to OC_8H_{17} chain), 4.02 (t, J = 7.0 Hz, 2H, OCH_2), 1.85 (m, 2H, OCH_2CH_2), 1.43 (m, 12H, alkyl chain), 0.90 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300.0 K): δ = 198.67, 157.65, 137.90, 137.83, 136.19, 132.82, 129.44, 129.26, 128.82, 114.63, 100.87, 68.08, 40.61, 31.80, 29.35, 29.22, 26.05, 22.64, 14.07.

‡ *Crystallographic data* for 4′-(4-octyloxyphenyl)-4,2′:6′,4″-terpyridine: $C_{29}H_{31}N_3O$ crystals suitable for structural analysis were grown from EtOH. A yellow prism (dimensions 0.18, 0.14, 0.12 mm) was mounted with oil on a thin quartz fiber. The molecular structure is largely unexceptional with an absence of both directional H-bonding and π-stacking of the aromatics. Monoclinic, space group, *C*2/*c*, a = 19.7473(3), b = 10.8189(3), c = 23.8391(7) Å, β = 114.033(1)°, V = 4651.57 Å^3, D_c = 1.2496 g cm^{-3}, Mo-Kα radiation (λ = 0.71073 Å) for Z = 2. Least-squares refinement based on 59925 reflections with $I_{net} > 3\sigma(I_{net})$ (out of 293 unique reflections) led to final value of R = 0.0625.

The intensity data was collected at 123 K using a Enraf-Nonius KappaCCD diffractometer. The structure was solved by direct methods using SHELXS and refined using SHELXL software. Crystallographic data have been deposited with the CCDC (12 Union Road, Cambridge, CB2 1EZ, UK) and are available on request quoting the deposition number CCDC 182/1797). See http://www.rsc.org/suppdata/cc/b0/b007431o/ for crystallographic files in .cif format.

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