

Article

Synthesis of Terpyridines: Simple Reactions—What Could Possibly Go Wrong?

Dalila Rocco, Catherine E. Housecroft  and Edwin C. Constable * 

University of Basel, Department of Chemistry, BPR 1096, Mattenstrasse 24a, CH-4058 Basel, Switzerland; dalila.rocco@unibas.ch (D.R.); catherine.housecroft@unibas.ch (C.E.H.)

* Correspondence: edwin.constable@unibas.ch; Tel.: +41-61-207-1001

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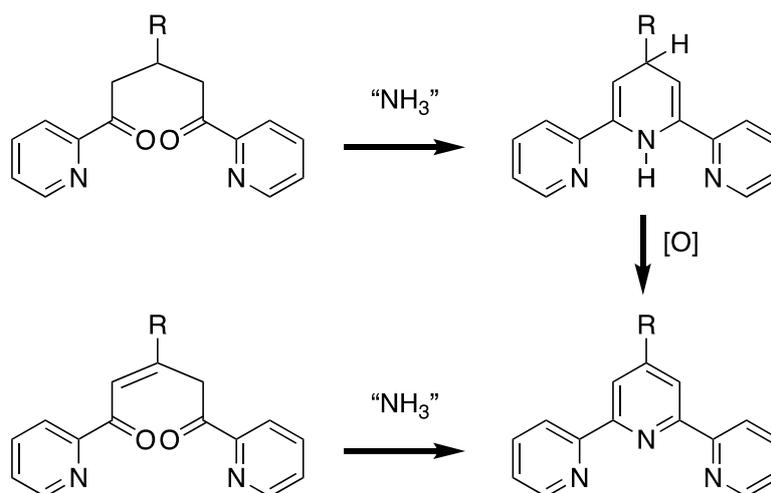
Abstract: The preparation of 2⁴-functionalized 1²,2²:2⁶,3²-terpyridines (4'-functionalized 3,2:6',3''-terpyridines) by the reaction of three 4-alkoxybenzaldehydes with 3-acetylpyridine and ammonia was investigated; under identical reaction conditions, two (R = ⁿC₄H₉, C₂H₅) gave the expected products whereas a third (R = ⁿC₃H₇) gave only a cyclohexanol derivative derived from the condensation of three molecules of 3-acetylpyridine with two of 4-(*n*-propoxy)benzaldehyde. A comprehensive survey of “unexpected” products from reactions of ArCOCH₃ derivatives with aromatic aldehydes is presented. Three different types of alternative product are identified.

Keywords: terpyridines; 3,2':6',3''-terpyridine; cyclohexanol derivative; condensation; heterocyclic

1. Introduction

The 48 isomeric structures obtained by the linking together of three pyridine rings by three single bonds are known collectively as the terpyridines [1]. One of the commonest metal-binding scaffolds encountered in supramolecular and materials chemistry is 2,2':6',2''-terpyridine (1, 2,2':6',2''-tpy) [2–7]: Note that in this article, we use the nomenclature that is established in the community for the terpyridines, rather than the preferred IUPAC names (PINs) of 1²,2²:2⁶,3²-terpyridine, 1³,2²:2⁶,3³-terpyridine and 1⁴,2²:2⁶,3⁴-terpyridine for 2,2':6',2''-terpyridine, 3,2':6',3''-terpyridine and 4,2':6',4''-terpyridine respectively [8]. Although the high kinetic and thermodynamic stability of 2,2':6',2''-tpy complexes confers unique properties, the main reason why this metal-binding domain is so commonly observed is the ease of synthesis of derivatives with a wide variety of substituents, in particular at the 4'-position of the central ring.

Although a vast array of synthetic strategies have been developed for the preparation of 2,2':6',2''-tpy derivatives, the majority are based upon the synthesis of an intermediate 1,5-bis(pyridin-2-yl)pentane-1,5-dione or 1,5-bis(pyridin-2-yl)pent-2-ene-1,5-dione (or their synthetic equivalents) which are subsequently cyclized to generate the central pyridine ring by reaction with a source of ammonia. Although the 1,5-bis(pyridin-2-yl)pent-2-ene-1,5-dione is at the correct oxidation state for the formation of the pyridine upon cyclization, the 1,5-bis(pyridin-2-yl)pentane-1,5-dione yields a 1',2'- or 1',4'-dihydro-2,2':6',2''-terpyridine which formally requires oxidation to the desired 2,2':6',2''-tpy (Scheme 1).



Scheme 1. The typical synthetic strategy for a 2,2':6',2''-tpy involves the cyclization of 1,5-bis(pyridin-2-yl)pentane-1,5-dione or 1,5-bis(pyridin-2-yl)pent-2-ene-1,5-dione or equivalent with ammonia. In the case of the 1,5-bis(pyridin-2-yl)pentane-1,5-dione, the intermediate dihydro-compound (the 1',4'-dihydro-2,2':6',2''-terpyridine is shown) requires an oxidation to generate the 2,2':6',2''-tpy.

The most common implementations of this strategy are based on the approach of Kröhnke (Scheme 2) [9]. In the classical Kröhnke synthesis, an intermediate enone (with the trivial name *chalcone* when two aromatic substituents are present [10]) obtained from the Claisen-Schmidt condensation [11,12] of 2-acetylpyridine with an aromatic aldehyde is reacted with an ammonia source and a “2-pyridacylpyridinium” salt; the latter is conveniently obtained by the Ortoleva-King reaction of 2-acetylpyridine with pyridine and iodine [13–15]. A convenient alternative is the direct reaction of two equivalents of 2-acetylpyridine with the aromatic aldehyde to give the 4-aryl-1,5-bis(pyridin-2-yl)pentane-1,5-dione directly or sequentially via the chalcone. Particularly attractive variations are solvent-free (or benign solvent) reactions and one-pot syntheses in which the reactants and an ammonia source, often ammonia and/or ammonium acetate are reacted directly or sequentially with the aromatic aldehyde and an acetylpyridine [16–20]. By replacing the 2-acetylpyridine by 3-acetylpyridine or 4-acetylpyridine, the synthetic approaches are readily adapted to the preparation of the symmetrical terpyridine isomers 3,2':6',3''-terpyridine (**2**, 3,2':6',3''-tpy, 1³,2²:2⁶,3³-terpyridine) and 4,2':6',4''-terpyridine (**3**, 4,2':6',4''-tpy, 1⁴,2²:2⁶,3⁴-terpyridine) (Figure 1). Although 2,2':6',2''-tpy is the most common motif encountered in coordination chemistry, 3,2':6',3''-tpy and 4,2':6',4''-tpy are increasingly finding application in the metal-directed formation of coordination networks [21–24]. In coordination networks incorporating 3,2':6',3''-tpy and 4,2':6',4''-tpy, the nitrogen atom of the central pyridine ring (ring 2 in the IUPAC recommendation), is never coordinated to a metal ion.

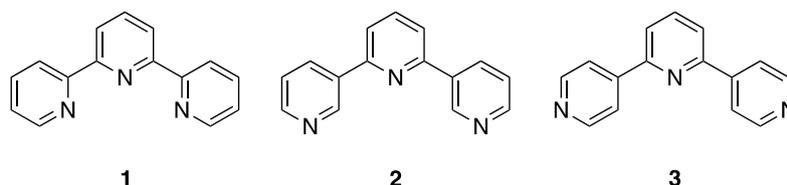
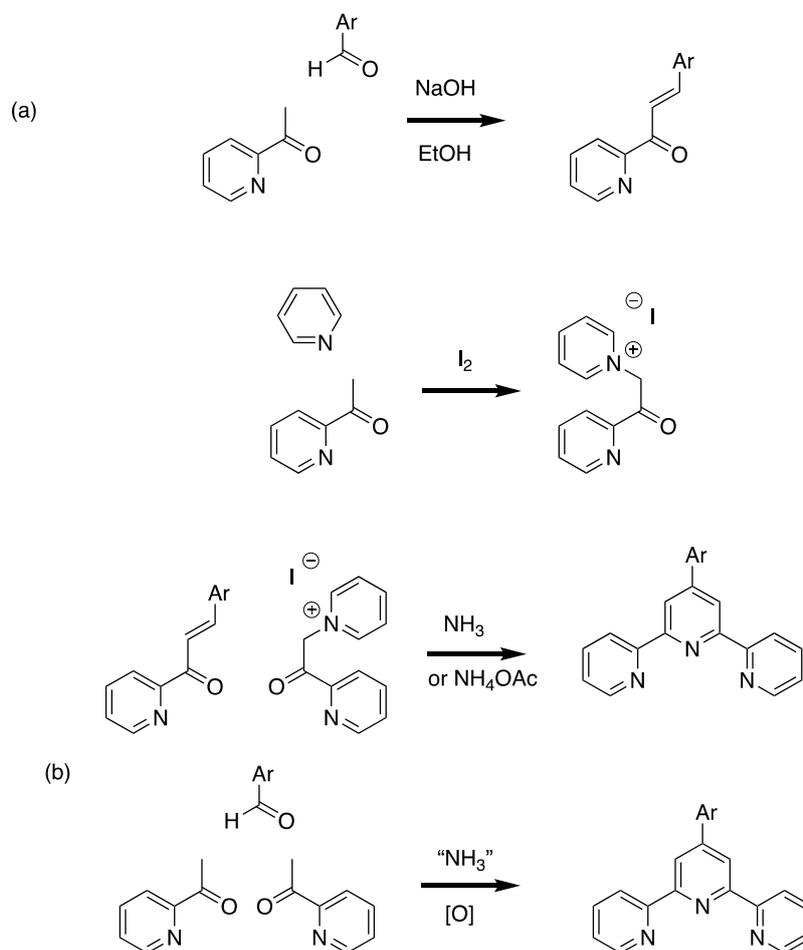


Figure 1. The structure of the most commonly encountered terpyridine, 2,2':6',2''-terpyridine (**1**), together with the closely related compounds 3,2':6',3''-terpyridine (**2**) and 4,2':6',4''-terpyridine (**3**).

In this paper, we discuss the synthesis of a series of 3,2':6',3''-tpy ligands (Figure 2) and describe the formation of an unexpected product in one case. The paper also provides a comprehensive review of alternative products which have been obtained from syntheses of terpyridines using the synthetic

approaches above. We take this opportunity to issue a *caveat*: when utilizing these synthetic methods, the terpyridine products should be purified and fully characterized.



Scheme 2. Variations on the Kröhnke reaction for the preparation of 4'-aryl-2,2':6',2''-tpy ligands. (a) The classical Kröhnke route in which an enone (chalcone) is prepared from the aldol condensation of 2-acetylpyridine with an aromatic aldehyde followed by reaction with a "2-pyridacylpyridinium" salt (obtained from an Ortoleva-King reaction) in the presence of an ammonia source (often ammonium acetate) to give the 4'-aryl-2,2':6',2''-tpy. (b) The simpler "one-pot" approach in which two equivalents of 2-acetylpyridine and the aromatic aldehyde are reacted directly or sequentially with a source of ammonia. This latter reaction may be in solvent free-conditions by grinding the reactants, use benign solvents such as PEG or conventional solvents. Replacement of the 2-acetylpyridine by 3-acetylpyridine or 4-acetylpyridine allows the synthesis of 4'-aryl-3,2':6',3''-tpy and 4'-aryl-4,2':6',4''-tpy ligands.

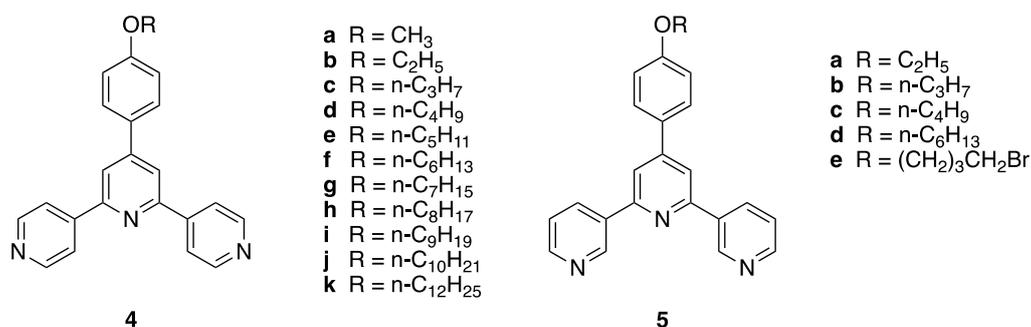


Figure 2. Structures of 4'-(4-alkyloxyphenyl)-4,2':6',4''-terpyridines and 4'-(4-alkyloxyphenyl)-3,2':6',3''-terpyridines. Compounds 5a–c are the subject of this publication.

2. Results and Discussion

2.1. Strategy and Ligand Design

We have shown that in the 4,2':6',4''-tpy compounds **4a–k** ($R = n\text{-C}_n\text{H}_{2n+1}$, $n = 1\text{--}10, 12$, Figure 2), the length of the alkyl chain on the alkyloxy substituent can influence the packing and the topology of coordination networks generated upon reaction with metal salts [22,25–30]. We are now beginning a systematic investigation of the effect of substituents on the assembly of coordination networks based on 3,2':6',3''-tpy ligands and commenced with the synthesis of derivatives **5a–c**. Compound **5d** has previously been reported [31]. The synthetic approach was a standard one-pot synthesis, involving the reaction of 3-acetylpyridine with the appropriate 4-alkyloxybenzaldehyde in basic solution, followed by the addition of aqueous ammonia.

2.2. Results

2.2.1. 4'-(4-Ethoxyphenyl)-3,2':6',3''-terpyridine and 4'-(4-butoxyphenyl)-3,2':6',3''-terpyridine

4'-(4-Ethoxyphenyl)-3,2':6',3''-terpyridine (**5a**) and 4'-(4-butoxyphenyl)-3,2':6',3''-terpyridine (**5c**) (Figure 3) were prepared following the one-pot method of Wang and Hanan [18]. 4-Ethoxybenzaldehyde or 4-butoxybenzaldehyde were reacted with 3-acetylpyridine in EtOH in the presence of KOH. After addition of aqueous NH_3 , **5a** and **5c** precipitated over a period of about 16 h as white solids in 16.7 and 31.1% yields, respectively.

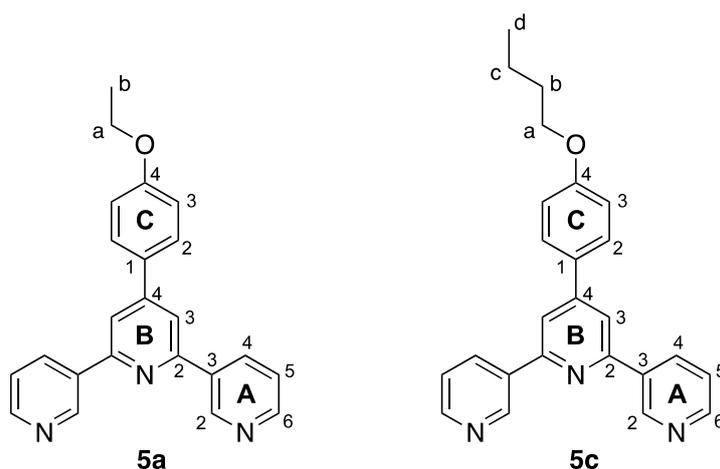


Figure 3. Structures of compounds **5a** and **5c** with atom labelling for NMR spectroscopic assignments.

The electrospray (ESI) mass spectra of compounds **5a** and **5c** showed base peaks at m/z 354.08 and 382.16, respectively, arising from the $[M + H]^+$ ions (Figures S1 and S2, see Supporting Information). The solution ^1H and ^{13}C NMR spectra were consistent with the structures shown in Figure 3 and were assigned using COSY, NOESY, HMQC and HMBC methods. Figure 4 displays a comparison of the ^1H NMR spectra, and confirms that the introduction of the different alkyloxy substituents has no significant influence on the spectroscopic signature of the 4'-phenyl-3,2':6',3''-tpy unit. $^{13}\text{C}\{^1\text{H}\}$ NMR spectra are compared in Figure S3. As expected, the solid-state IR spectra of **5a** and **5c** are very similar (Figures S4 and S5) and the solution absorption spectra (Figure 5) show intense absorptions in the UV region arising from spin-allowed $\pi^* \leftarrow \pi$ and $\pi^* \leftarrow n$ transitions.

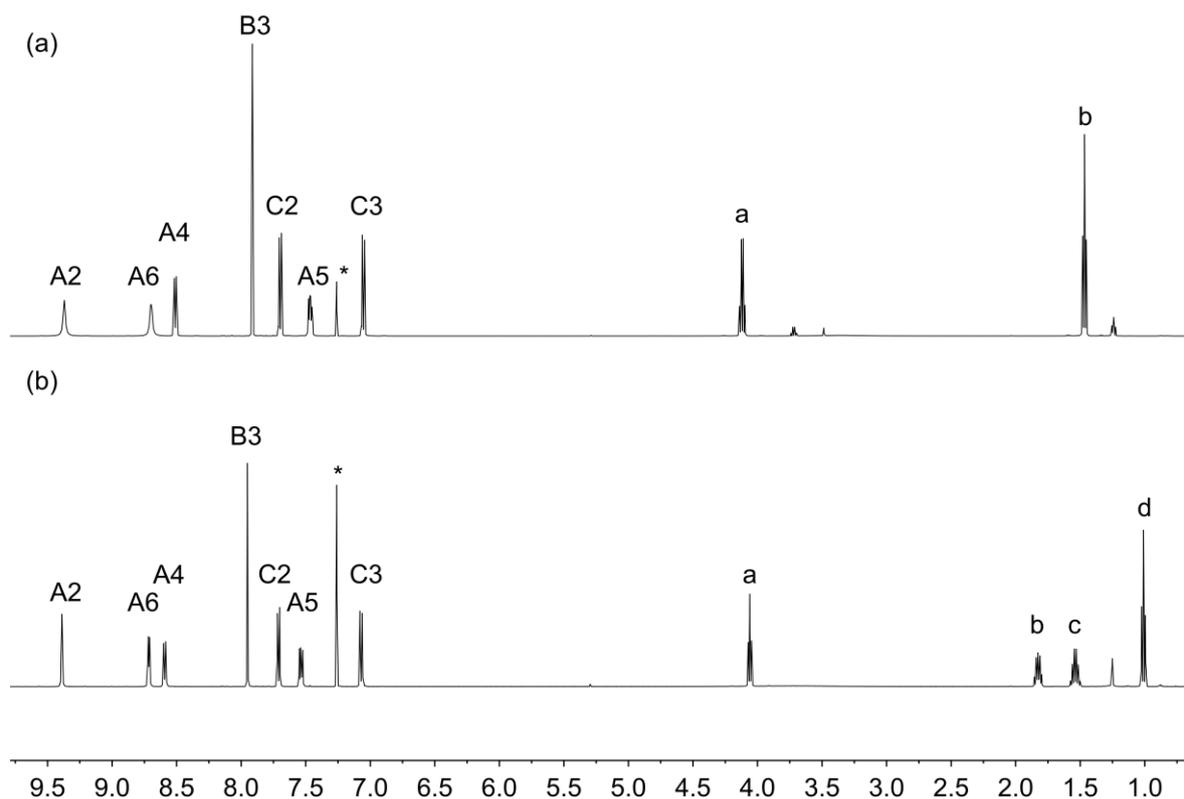


Figure 4. ^1H NMR spectra (500 MHz, CDCl_3 , 298 K) of (a) **5a** and (b) **5c**. See Figure 3 for the atom labelling scheme. * = residual CHCl_3 .

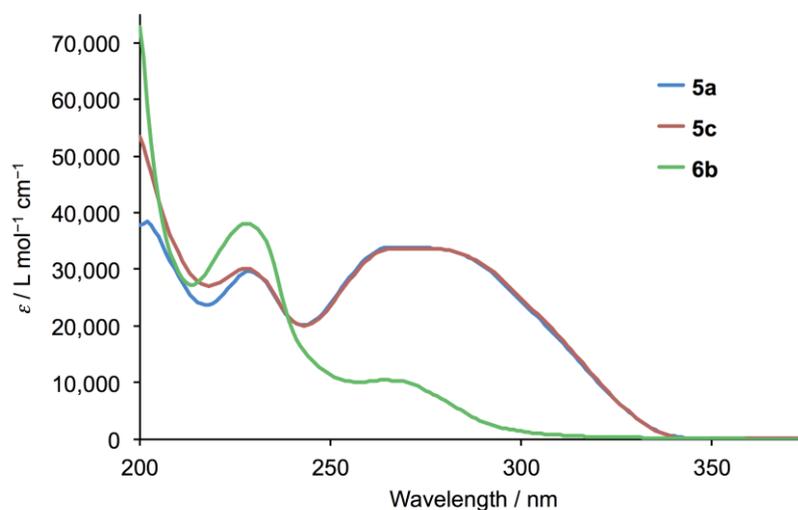


Figure 5. Solution absorption spectra of **5a**, **5c** and **6b** (MeCN , $3.3 \times 10^{-5} \text{ mol dm}^{-3}$).

2.2.2. A Reaction that Works with Ethoxy and Butoxy Homologues, Fails for 4'-(4-propoxyphenyl)-3,2':6',3''-terpyridine

During attempts to prepare 4'-(4-propoxyphenyl)-3,2':6',3''-terpyridine (**5b**, Figure 2) by the reaction of 4-propoxybenzaldehyde with 3-acetylpyridine in the presence of KOH in ethanol, under identical conditions to those for the successful preparation of ligands **5a** and **5c**, followed by addition of aqueous NH_3 , we noted that precipitation of a product began before ammonia was added. The white solid that was isolated exhibited IR (Figure S6) and absorption spectra (Figure 5) with different profiles from those of **5a** and **5c**. In particular, the IR spectrum of the product exhibited a sharp absorption at 3495 cm^{-1} attributable to an OH group. These observations were unexpected since we have previously

reported the successful synthesis of the analogous series of 4,2':6',4''-tpy derivatives **4a–4k** (Figure 2) by the Hanan one-pot strategy [25]. The ESI mass spectrum of the product showed a base peak at m/z 656.31 (Figure S7) suggesting the formation of the cyclic product **6** shown in Figure 6.

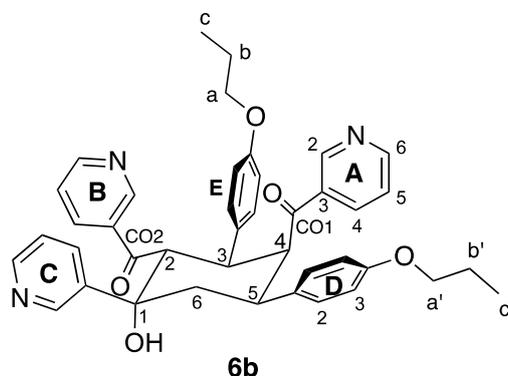


Figure 6. Structure of compound **6b** with atom labelling for NMR spectroscopic assignments.

The solution ^1H NMR spectrum of **6b** is shown in Figure 7 and is consistent with the presence of three pyridine environments (rings A, B and C) and two 4-propoxyphenyl environments (rings D and E). The spectrum was assigned using COSY, NOESY (Figure S8), HMQC (Figure S9) and HMBC (Figure S10) methods with critical NOESY crosspeaks being between $\text{H}^{\text{OH}}/\text{H}^{\text{C}2}$, $\text{H}^{\text{D}3}/\text{H}^{\text{a}'}$, $\text{H}^{\text{E}3}/\text{H}^{\text{a}}$, $\text{H}^{\text{D}2}/\text{H}^5$, $\text{H}^{\text{D}2}/\text{H}^{\text{6ax}}$, $\text{H}^{\text{E}2}/\text{H}^3$ and $\text{H}^{\text{E}2}/\text{H}^2$.

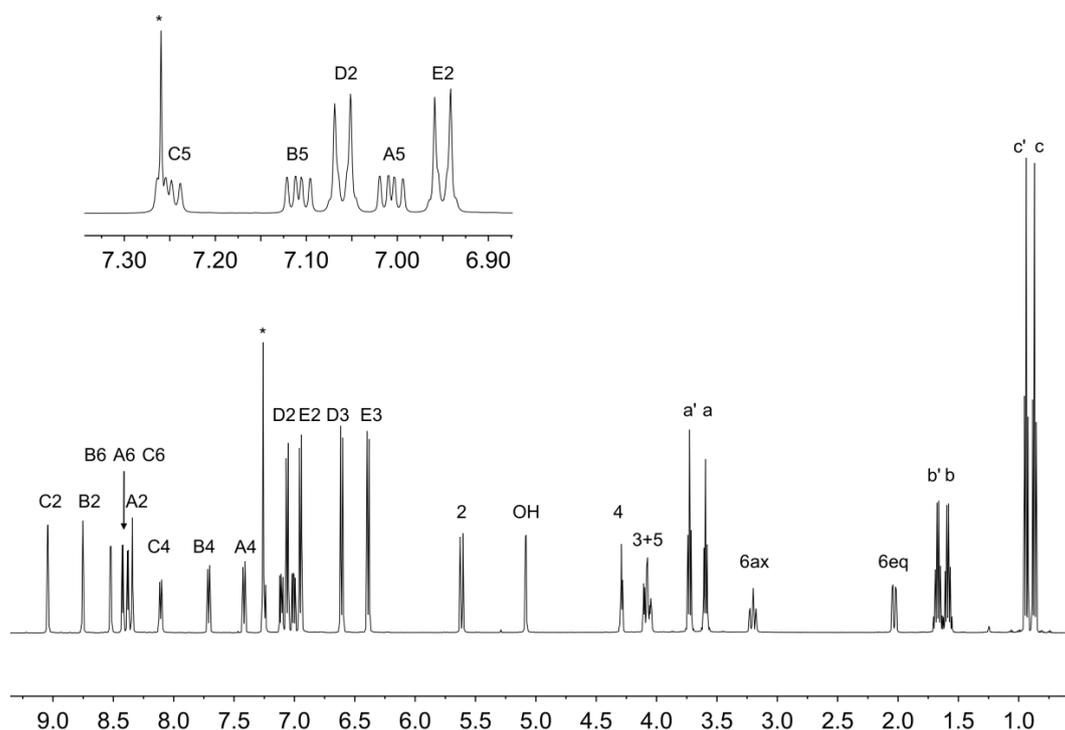


Figure 7. ^1H NMR spectrum (500 MHz, CDCl_3 , 298 K) of compound **6b**. See Figure 6 for atom labelling. * = residual CHCl_3 .

The spectroscopic characterization confirms the formation of **6b** although it offers no indication as to why this product precipitates from solution only in the case of the propoxy substituent. We noted that the reaction only involves the aldehyde and the 3-acetylpyridine and were prompted to perform the reactions in the absence of ammonia. We repeated the reaction of 4-propoxybenzaldehyde with 3-acetylpyridine at a 1:2 molar ratio in ethanol with KOH but without the addition of NH_3 . This led to

the formation of **6b** (confirmed by NMR spectroscopy, Figure 8b) in 42.0% yield. We then performed the analogous reactions of 4-ethoxybenzaldehyde or 4-butoxybenzaldehyde with 3-acetylpyridine in the presence of KOH in ethanol, but without NH₃. In both cases, white precipitates formed within 5 min. The ESI mass spectra of the products were consistent with their being analogues of **6b**. Base peaks at $m/z = 628.29$ and 684.35 were assigned to [**6a** + H]⁺ and [**6c** + H]⁺, respectively (Figures S11 and S12). The ¹H NMR spectra of **6a** and **6c** are shown in Figure 8a,c, and the similarity to that of **6b** (Figure 8b) is immediately apparent. The ¹H and ¹³C NMR spectra of **6a** and **6c** (see Experimental Section) were assigned using routine 2D methods.

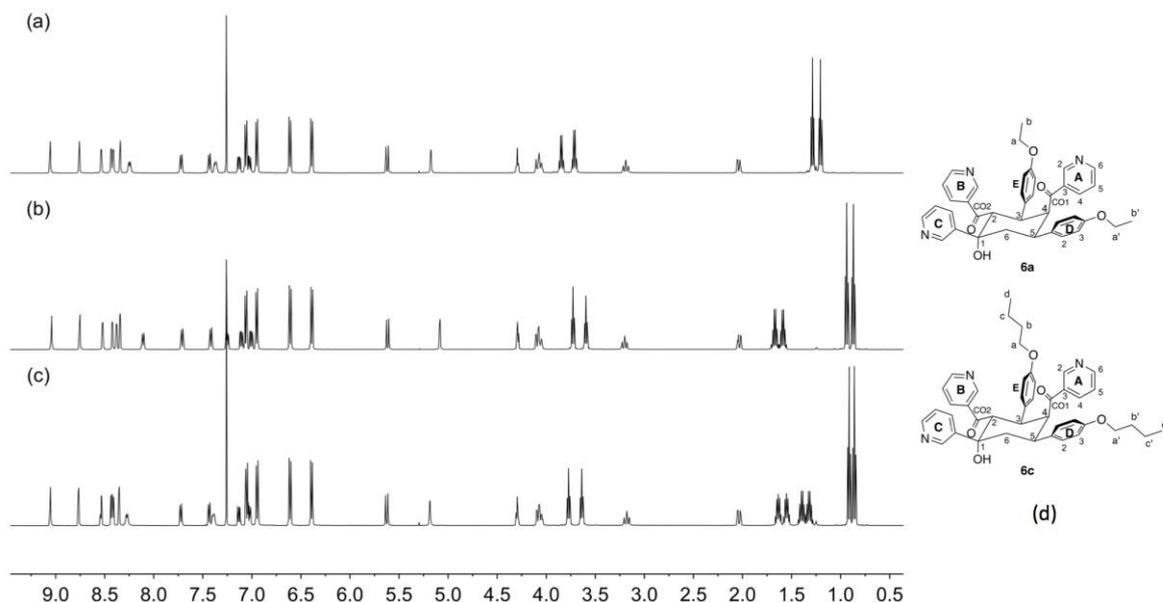


Figure 8. A comparison of the ¹H NMR (500 MHz, CDCl₃, 298 K) spectra of the cyclic products (a) **6a**, (b) **6b** and (c) **6c**. The singlet at δ 7.26 ppm in each spectrum is residual CHCl₃. (d) The structures of **6a** and **6c** with atom labelling for NMR spectroscopic assignments (see Sections 4.5 and 4.6).

3. Review of Literature

3.1. Introduction

Although the Claisen-Schmidt condensation is presented as a simple reaction with a hydroxyketone intermediate and a single enone product in many chemistry text books, the reality is often far more complex. Although this paper is concerned with the use of acetylpyridines in the Claisen-Schmidt reaction, it is instructive to review the broader literature regarding the condensation of aromatic aldehydes with aromatic ketones.

The enone products of the Claisen-Schmidt reaction are electrophilic and can react with nucleophilic enols or enolates at either the carbonyl carbon or by conjugate addition. The formation of the enone 1:1 products (1:1 ratio of ketone to aldehyde) involves the nucleophilic attack of an enol or enolate derived from the aromatic ketone upon the aromatic aldehyde. A number of publications have provided overviews of the reaction space and the types of products that are to be expected. If the rates of the subsequent reactions are significantly faster than the initial ones leading to the enone, domino [32–34] or tandem [35] reactions are expected, leading to the selective formation of one (or more) of a range of potential reaction products. In this section, we present a comprehensive overview of the products other than terpyridines that have been obtained from Kröhnke and related syntheses. We have already considered products of this type implicitly—the pentane-1,5-diones (**7**) arise from the addition of a second equivalent enol or enolate to the enone, giving products of 2:1 (ketone to aldehyde) stoichiometry (Figure 9).

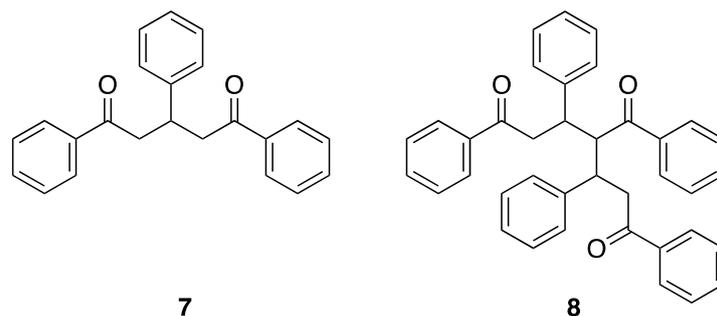


Figure 9. The structure of the 2:1 (ketone:aldehyde) pentane-1,5-dione that can arise from the reaction of acetophenone with benzaldehyde and the proposed structure of Kostanecki's triketone the 3:2 adduct that formally arises from the nucleophilic addition of the enol of enolate of the pentane-1,5-dione on the 1:1 enone.

3.2. The 3:2 Products

The most common of the products that have been isolated from attempted terpyridine syntheses have a reactant stoichiometry of 3:2 ketone-aldehyde. In one respect, this is an old story dating back to 1892 when the compound claimed to be Kostanecki's triketone (**8**) was isolated as a product from the reaction of benzaldehyde and acetophenone [36]. Over the years, a number of materials purporting to be **8**, but possessing different physical properties have been reported [37,38]. A definitive report of the preparation and structural characterization of **8** describing the history of this compound together with an analysis of the various products isolated from the reaction of acetophenone with benzaldehyde appeared recently [39]. A large number of 3:2 condensation products have now been fully characterized by structural and spectroscopic means and shown to be cyclohexanols **9** arising from formally from the internal condensation of intermediate triketones. Naming the compounds as cyclohexanols for consistency (the IUPAC PIN is based upon 4-hydroxycyclohexane-1,3-diy)bis(methanone)), the relative stereochemistry is $1R^*, 2S^*, 3R^*, 5R^*$: the substituent in the 4-position may be either axial or equatorial giving both $4R^*$ and $4S^*$ ($4-R^*$ **9** or $4-S^*$ **9**, Figure 10). The cyclic product is obtained in particularly high yield under phase transfer conditions from the reaction of benzaldehyde and acetophenone [40]. The reaction of enones with NaO^tBu and *N*-heterocyclic carbenes, yielded **9** and aldehyde [41]. A significant range of compounds with various Ar and Ar₁ groups have been characterized, from one pot reactions of ArCHO and Ar₁COCH₃ or from sequential reactions of isolated enones. In addition to the parent compound (Ar = Ar₁ = C₆H₅) [39–46], a large number of derivatives with carbocyclic Ar and Ar₁ substituents have been obtained from reactions of substituted benzaldehydes and acetophenones [34,41,43,46–53]. Of most relevance to the chemistry reported in this manuscript, are compounds with heterocyclic substituents and, to date, examples with thiophen-2-yl [34,41,54–56], furan-2-yl [54,57], benzofuran-2-yl [33], benzofuran-3-yl [33], benzothiophen-2-yl [33], benzothiophen-3-yl [33], pyridin-2-yl [33,35,45,58–66] pyridin-3-yl [33,45,56] and pyridin-4-yl [16,20,33,45,56,67] groups have been reported. Cave and Raston have commented that reactions of 4-acetylpyridine with 4-alkoxybenzaldehydes in solution only yield the 3:2 products rather than the desired 4,2':6',4''-terpyridines [16,20]. We note, however, that in our hands and under the Hanan one-pot procedure [18], the 4'-(4-alkoxy)-4,2':6',4''-terpyridines shown in Figure 2 can be readily prepared [25].

To summarize, the formation of 3:2 condensation products is well-established with the stereochemistry at four of the five stereogenic centres defined. Examples of diastereoisomers with the 4-substituent in the axial or equatorial positions have been described and the less stable axial *R* diastereoisomer may be converted to the more stable equatorial *S* form with base [58].

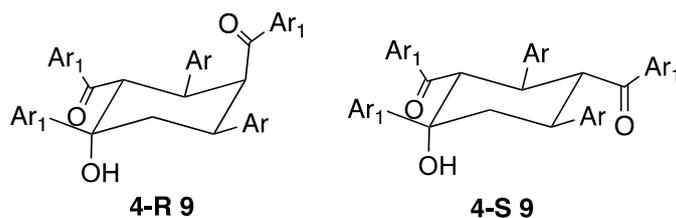


Figure 10. The structures of the 3:2 cyclohexanol derivatives arising from the cyclization of the triketones.

3.3. The 3:1 Products

A second type of cyclohexane derivative **10** (Figure 11) with a 3:1 (ketone-aldehyde) constitution is also known. We first described the formation of cyclohexane-1,3-diols from the condensation of 2-acetylpyridine with benzaldehyde derivatives in 1995 [58]. Although less commonly observed than the 3:2 condensation products, compounds of this type, arising from the aldol condensation of an intermediate pentane-1,5-dione with a third equivalent of ketone, have been isolated with a variety of substituents [32,60,68–73]. The relative stereochemistry in **10**, originally proposed on the basis of NMR studies [58], has been crystallographically confirmed [32,69,70,72]. Sequential reaction of the benzaldehyde derivative with two different ketones, Ar_1COCH_3 and Ar_2COCH_3 allows the synthesis of compounds **11** via the addition of Ar_2COCH_3 to the intermediate enone $\text{Ar}_1\text{COCH}=\text{CHAr}$.

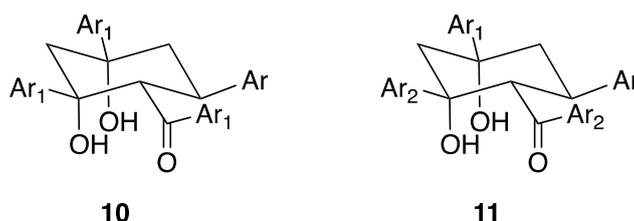
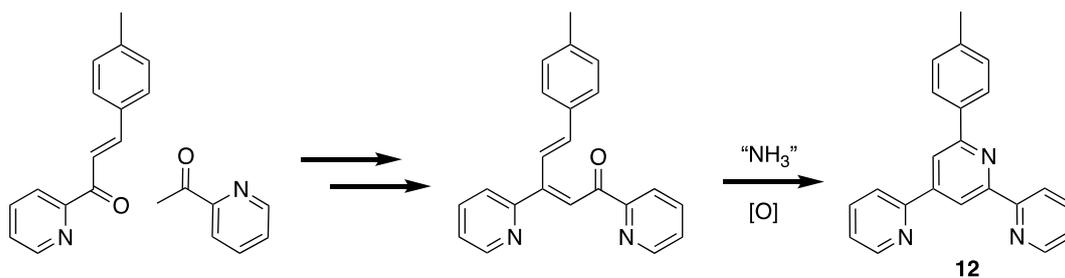


Figure 11. The structures of the 3:1 cyclohexane-1,3-diol derivatives arising from the condensation of the pentane-1,5-dione with Ar_1COCH_3 .

3.4. An Unexpected Terpyridine Isomer

A third type of unexpected product obtained from attempted 4'-aryl-2,2':6',2''-terpyridine syntheses is the isomeric 6'-aryl-2,2':4',2''-terpyridine. This was first observed when 6'-(4-methylphenyl)-2,2':4',2''-terpyridine (**12**) was isolated as a side-product from the condensation of 2-acetylpyridine with 4-methylbenzaldehyde and ammonia [74–80]. This product presumably arises by the 1,2-attack of the enol or enolate of 2-acetylpyridine at the carbonyl (rather than the more usual 1,4-conjugate addition) of the intermediate enone, 3-(4-methylphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (Scheme 3). Similarly, the preparation of 4'-phenyl-4,2':6',4''-terpyridine from 4-acetylpyridine and benzaldehyde gave appreciable amounts of 6'-(4-methylphenyl)-4,2':4',4''-terpyridine (**12**) [81].



Scheme 3. The origin of the isomeric 2,2':4',2''-terpyridine in 2,2':6',2''-terpyridine synthesis.

4. Materials and Methods

^1H and ^{13}C and NMR spectra were recorded on a Bruker Avance III-500 spectrometer (Bruker BioSpin AG, Fällanden, Switzerland) at 298 K. The ^1H and ^{13}C NMR chemical shifts were referenced with respect to residual solvent peaks (δ TMS = 0) and all quoted coupling constants J are J_{HH} between protons. A Shimadzu LCMS-2020 instrument (Shimadzu Schweiz GmbH, Roemerstr., Switzerland) was used to record electrospray ionization (ESI) mass spectra; samples were introduced as 200–800 μM solutions in MeCN with the addition of formic acid. PerkinElmer UATR Two (Perkin Elmer, Bahnstrasse 8, 8603 Schwerzenbach, Switzerland) and Cary-5000 (Agilent Technologies Inc., Santa Clara, CA, United States) spectrometers were used to record FT-infrared (IR) and absorption spectra, respectively. Melting points were measured using a Bibby Melting Point Apparatus SMP30.

3-Acetylpyridine was purchased from Acros Organics (Chemie Brunschwig AG, Basel, Switzerland), 4-ethoxybenzaldehyde and 4-butoxybenzaldehyde from Sigma Aldrich (Riedstr. 2, 89555 Steinheim, Germany), and 4-propoxybenzaldehyde from Fluorochem and were used as received.

4.1. Compound 5a

4-Ethoxybenzaldehyde (1.50 g, 1.39 mL, 10.0 mmol) was dissolved in EtOH (50 mL), then 3-acetylpyridine (2.42 g, 2.20 mL, 20.0 mmol) and crushed KOH (1.12 g, 20.0 mmol) were added to the solution. Aqueous NH_3 (32%, 38.5 mL) was slowly added to the reaction mixture. This was stirred at room temperature overnight. The solid that formed was collected by filtration, washed with water (3×10 mL) followed by EtOH (3×10 mL), recrystallized from EtOH and dried *in vacuo*. Compound 5a was isolated as a white powder (0.591 g, 1.67 mmol, 16.7%). M.p. = 120 °C. ^1H NMR (500 MHz, CDCl_3): δ/ppm = 9.37 (m, 2H, $\text{H}^{\text{A}2}$), 8.70 (m, 2H, $\text{H}^{\text{A}6}$), 8.51 (8.51 (dt, J = 8.0, 1.9 Hz, 2H, $\text{H}^{\text{A}4}$), 7.91 (s, 2H, $\text{H}^{\text{B}3}$), 7.70 (m, 2H, $\text{H}^{\text{C}2}$), 7.47 (m, 2H, $\text{H}^{\text{A}5}$), 7.05 (m, 2H, $\text{H}^{\text{C}3}$), 4.12 (q, J = 7.0 Hz, 2H, H^{a}), 1.47 (t, J = 7.0 Hz, 3H, H^{b}). $^{13}\text{C}\{^1\text{H}\}$ NMR (500 MHz, CDCl_3): δ/ppm = 160.1 ($\text{C}^{\text{C}4}$), 155.0 ($\text{C}^{\text{A}3}$), 150.3 ($\text{C}^{\text{B}4}$), 149.7 ($\text{C}^{\text{A}6}$), 148.0 ($\text{C}^{\text{A}2}$), 134.8 ($\text{C}^{\text{A}4}$), 134.6 ($\text{C}^{\text{B}2}$), 130.0 ($\text{C}^{\text{C}1}$), 128.2 ($\text{C}^{\text{C}2}$), 123.6 ($\text{C}^{\text{A}5}$), 117.1 ($\text{C}^{\text{B}3}$), 115.1 ($\text{C}^{\text{C}3}$), 63.6 (C^{a}), 14.7 (C^{b}). UV-VIS (CH_3CN , 3.3×10^{-5} mol dm^{-3}) λ/nm 229 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 29,700), 272 (33,800). ESI-MS m/z 354.08 [$\text{M} + \text{H}$] $^+$ (calc. 354.16). Found C 77.38, H 5.30, N 11.91; required for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}$: C 78.16, H 5.42, N 11.89.

4.2. Compound 5c

4-Butoxybenzaldehyde (1.78 g, 1.73 mL, 10.0 mmol) was dissolved in EtOH (50 mL), then 3-acetylpyridine (2.42 g, 2.20 mL, 20.0 mmol) and crushed KOH (1.12 g, 20.0 mmol) were added to the solution. Aqueous NH_3 (32%, 38.5 mL) was slowly added to the reaction mixture. This was stirred at room temperature overnight. The solid that formed was collected by filtration, washed with water (3×10 mL) and EtOH (3×10 mL), then recrystallized from EtOH and dried *in vacuo*. Compound 5c was isolated as a white powder (1.19 g, 3.11 mmol, 31.1%). M.p. = 113 °C. ^1H NMR (500 MHz, CDCl_3): δ/ppm = 9.39 ((d, J = 2.2 Hz, 2H, $\text{H}^{\text{A}2}$), 8.72 ((dd, J = 4.9, 1.6 Hz, 2H, $\text{H}^{\text{A}6}$), 8.59 (dt, J = 8.1, 2.0 Hz, 2H, $\text{H}^{\text{A}4}$), 7.95 (s, 2H, $\text{H}^{\text{B}3}$), 7.71 (m, 2H, $\text{H}^{\text{C}2}$), 7.53 (m, 2H, $\text{H}^{\text{A}5}$), 7.07 (m, 2H, $\text{H}^{\text{C}3}$), 4.06 (t, J = 6.5 Hz, 2H, H^{a}), 1.83 (m, 2H, H^{b}), 1.54 (m, 2H, H^{c}), 1.01 (t, J = 7.4 Hz, 3H, H^{d}). $^{13}\text{C}\{^1\text{H}\}$ NMR (500 MHz, CDCl_3): δ/ppm = 160.8 ($\text{C}^{\text{C}4}$), 154.9 ($\text{C}^{\text{A}3}$), 150.9 ($\text{C}^{\text{B}4}$), 149.0 ($\text{C}^{\text{A}6}$), 147.4 ($\text{C}^{\text{A}2}$), 135.8 ($\text{C}^{\text{A}4}$), 135.4 ($\text{C}^{\text{B}2}$), 129.9 ($\text{C}^{\text{C}1}$), 128.5 ($\text{C}^{\text{C}2}$), 124.2 ($\text{C}^{\text{A}5}$), 117.6 ($\text{C}^{\text{B}3}$), 115.5 ($\text{C}^{\text{C}3}$), 68.1 (C^{a}), 31.4 (C^{b}), 19.4 (C^{c}), 14.0 (C^{d}). UV-VIS (CH_3CN , 3.3×10^{-5} mol dm^{-3}) λ/nm 228 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 30,100), 274 (33,700). ESI-MS m/z 382.16 [$\text{M} + \text{H}$] $^+$ (calc. 382.19). Found C 78.37, H 5.93, N 11.05; required for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}$: C 78.71, H 6.08, N 11.02.

4.3. Compound 6b: Method 1

4-Propoxybenzaldehyde (1.64 g, 1.58 mL, 10.0 mmol) was dissolved in EtOH (50 mL), then 3-acetylpyridine (2.42 g, 2.20 mL, 20.0 mmol) and crushed KOH (1.12 g, 20.0 mmol) were added to the solution. At this stage, a white precipitate began to form. Aqueous NH_3 (32%, 38.5 mL) was slowly

added to the reaction mixture which was then stirred at room temperature overnight. The solid that formed was collected by filtration, washed with water (3 × 10 mL) then with EtOH (3 × 10 mL), and was recrystallized from EtOH and dried *in vacuo*. Compound **6b** was isolated as a white powder (0.495 g, 0.755 mmol, 15.1%). M.p. = 208 °C. ¹H NMR (500 MHz, CDCl₃): δ/ppm = 9.04 (d, *J* = 1.9 Hz, 1H, H^{C2}), 8.75 (d, *J* = 1.8 Hz, 1H, H^{B2}), 8.52 (dd, *J* = 4.8, 1.6 Hz, 1H, H^{B6}), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H, H^{A6}), 8.38 (dd, *J* = 4.8, 1.5 Hz, 1H, H^{C6}), 8.34 (d, *J* = 1.7 Hz, 1H, H^{A2}), 8.11 (dt, *J* = 8.1, 1.8 Hz, 1H, H^{C4}), 7.71 (dt, *J* = 8.1, 2.0 Hz, 1H, H^{B4}), 7.42 (dt, *J* = 8.1, 2.0 Hz, 1H, H^{A4}), 7.25 (m, 1H, H^{C5}), 7.11 (m, 1H, H^{B5}), 7.06 (m, 2H, H^{D2}), 7.01 (m, 1H, H^{A5}), 6.95 (m, 2H, H^{E2}), 6.61 (m, 2H, H^{D3}), 6.39 (m, 2H, H^{E3}), 5.62 (d, *J* = 11.9 Hz, 1H, H²), 5.08 (d, *J* = 2.1 Hz, 1H, H^{OH}), 4.29 (dd, *J* = 4.7, 4.7 Hz, 1H, H⁴), 4.08 (m, 2H, H³⁺⁵), 3.73 (m, 2H, H^{a'}), 3.60 (m, 2H, H^a), 3.20 (ddd, *J* = 13.0, 13.0, 2.5 Hz, 1H, H^{6ax}), 2.03 (dd, *J* = 13.7, 3.4 Hz, 1H, H^{6eq}), 1.67 (m, 2H, H^{b'}), 1.59 (m, 2H, H^b), 0.94 (t, *J* = 7.4 Hz, 3H, H^{c'}), 0.87 (t, *J* = 7.4 Hz, 3H, H^c). ¹³C{¹H} NMR (500 MHz, CDCl₃): δ/ppm = 206.8 (C^{CO2}), 206.1 (C^{CO1}), 158.3 (C^{E4}), 158.1 (C^{D4}), 153.7 (C^{B6}), 152.5 (C^{A6}), 149.6 (C^{B2}), 149.1 (C^{A2}), 147.9 (C^{C6}), 146.4 (C^{C2}), 142.6 (C^{C3}), 135.2 (C^{B4}), 135.0 (C^{A3}), 134.8 (C^{A4}), 133.8 (C^{C4}), 133.0 (C^{B3}), 132.7 (C^{D1}), 130.2 (C^{E1}), 129.7 (C^{E2}), 128.6 (C^{D2}), 123.5 (C^{C5}), 123.2 (C^{B5}), 122.9 (C^{A5}), 114.7 (C^{D3}), 114.6 (C^{E3}), 75.0 (C¹), 69.6 (C^{a'}), 69.4 (C^a), 53.5 (C⁴), 51.0 (C²), 46.8 (C³), 41.2 (C⁵), 38.8 (C⁶), 22.6 (C^{b'}), 22.5 (C^b), 10.6 (C^{c'}), 10.5 (C^c). UV-VIS (CH₃CN, 3.3 × 10⁻⁵ mol dm⁻³) λ/nm 228 (ε/dm³ mol⁻¹ cm⁻¹ 38,100), 264 (10,400). ESI-MS *m/z* 656.31 [M + H]⁺ (calc. 656.31). IR spectrum: see Figure S6. Found C 74.67, H 6.77, N 6.73; required for C₄₁H₄₁N₃O₅ C 75.09, H 6.30, N 6.41.

4.4. Compound **6b**: Method 2

The reaction was carried out as in method 1 without the addition of NH₃. Reagents and solvent: 4-propoxybenzaldehyde (0.82 g, 0.79 mL, 5.0 mmol), EtOH (25 mL), 3-acetylpyridine (1.21 g, 1.10 mL, 10.0 mmol) and crushed KOH (0.56 g, 10.0 mmol). **6b** was isolated as a white powder (0.690 g, 1.05 mmol, 42.0%). Characterization data matched those for the product reported in Section 4.3.

4.5. Compound **6a**

4-Ethoxybenzaldehyde (0.75 g, 0.70 mL, 5.0 mmol) was dissolved in EtOH (25 mL), then 3-acetylpyridine (1.21 g, 1.10 mL, 10.0 mmol) and crushed KOH (0.56 g, 10.0 mmol) were added to the solution. After five minutes a white precipitate began to form. The reaction mixture was stirred at room temperature overnight. The solid that formed was collected by filtration, washed with water (3 × 10 mL) then EtOH (3 × 10 mL), recrystallized from EtOH and dried *in vacuo*. **6a** was isolated as a white powder (0.268 g, 0.427 mmol, 17.1%). M.p. = 210 °C. ¹H NMR (500 MHz, CDCl₃): δ/ppm = 9.06 (d, *J* = 1.9 Hz, 1H, H^{C2}), 8.76 (d, *J* = 1.8 Hz, 1H, H^{B2}), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H, H^{B6}), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H, H^{A6}), 8.41 (dd, *J* = 4.9, 1.3 Hz, 1H, H^{C6}), 8.34 (d, *J* = 1.8 Hz, 1H, H^{A2}), 8.25 (m, 1H, H^{C4}), 7.72 (dt, *J* = 8.0, 1.9 Hz, 1H, H^{B4}), 7.43 (dt, *J* = 8.0, 1.9 Hz, 1H, H^{A4}), 7.37 (m, 1H, H^{C5}), 7.13 (m, 1H, H^{B5}), 7.05 (m, 2H, H^{D2}), 7.02 (m, 1H, H^{A5}), 6.95 (m, 2H, H^{E2}), 6.61 (m, 2H, H^{D3}), 6.39 (m, 2H, H^{E3}), 5.62 (d, *J* = 11.9 Hz, 1H, H²), 5.18 (d, *J* = 2.1 Hz, 1H, H^{OH}), 4.29 (dd, *J* = 4.6, 4.6 Hz, 1H, H⁴), 4.08 (m, 2H, H³⁺⁵), 3.85 (m, 2H, H^{a'}), 3.71 (m, 2H, H^a), 3.19 (ddd, *J* = 13.6, 13.6, 2.1 Hz, 1H, H^{6ax}), 2.04 (dd, *J* = 13.7, 3.4 Hz, 1H, H^{6eq}), 1.29 (t, *J* = 7.0 Hz, 3H, H^{b'}), 1.20 (t, *J* = 7.0 Hz, 3H, H^b). ¹³C{¹H} NMR (500 MHz, CDCl₃): δ/ppm = 206.6 (C^{CO2}), 206.1 (C^{CO1}), 158.2 (C^{E4}), 158.0 (C^{D4}), 153.9 (C^{B6}), 152.6 (C^{A6}), 149.6 (C^{B2}), 149.1 (C^{A2}), 146.2 (C^{C6}), 144.8 (C^{C2}), 143.2 (C^{C3}), 135.3 (C^{C4}), 134.8 (C^{A3}), 134.9 (C^{B4}), 134.8 (C^{A4}), 132.8 (C^{B3}), 132.6 (C^{D1}), 130.1 (C^{E1}), 129.7 (C^{E2}), 128.6 (C^{D2}), 123.5 (C^{C5}), 123.4 (C^{B5}), 123.0 (C^{A5}), 114.7 (C^{D3}), 114.6 (C^{E3}), 75.1 (C¹), 63.5 (C^{a'}), 63.2 (C^a), 53.4 (C⁴), 50.8 (C²), 46.9 (C³), 41.2 (C⁵), 38.9 (C⁶), 14.8 (C^{b'}), 14.7 (C^b). ESI-MS *m/z* 628.29 [M + H]⁺ (calc. 628.28). IR spectrum: see Figure S13. Found C 74.26, H 5.88, N 6.53; required for C₃₉H₃₇N₃O₅ C 74.62, H 5.94, N 6.69.

4.6. Compound **6c**

4-Butoxybenzaldehyde (0.89 g, 0.87 mL, 5.0 mmol) was dissolved in EtOH (25 mL), then 3-acetylpyridine (1.21 g, 1.10 mL, 10.0 mmol) and crushed KOH (0.56 g, 10.0 mmol) were added to the

solution. After five minutes a white precipitate began to form. The reaction mixture was stirred at room temperature overnight. The precipitate was collected by filtration, washed with water (3 × 10 mL) and EtOH (3 × 10 mL), then recrystallized from EtOH and dried in vacuo. **6c** was isolated as a white powder (0.399 g, 0.585 mmol, 11.7%). M.p. = 185 °C. ¹H NMR (500 MHz, CDCl₃): δ/ppm = 9.06 (d, *J* = 1.8 Hz, 1H, H^{C2}), 8.77 (d, *J* = 1.8 Hz, 1H, H^{B2}), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H, H^{B6}), 8.43 (dd, *J* = 4.8, 1.7 Hz, 1H, H^{A6}), 8.42 (dd, *J* = 5.0, 1.4 Hz, 1H, H^{C6}), 8.35 (d, *J* = 1.7 Hz, 1H, H^{A2}), 8.27 (m, 1H, H^{C4}), 7.72 (dt, *J* = 8.0, 1.9 Hz, 1H, H^{B4}), 7.44 (dt, *J* = 8.0, 2.0 Hz, 1H, H^{A4}), 7.39 (m, 1H, H^{C5}), 7.13 (m, 1H, H^{B5}), 7.05 (m, 2H, H^{D2}), 7.02 (m, 1H, H^{A5}), 6.95 (m, 2H, H^{E2}), 6.61 (m, 2H, H^{D3}), 6.39 (m, 2H, H^{E3}), 5.63 (d, *J* = 11.9 Hz, 1H, H²), 5.18 (d, *J* = 2.1 Hz, 1H, H^{OH}), 4.29 (dd, *J* = 4.6, 4.6 Hz, 1H, H⁴), 4.08 (m, 2H, H³⁺⁵), 3.77 (m, 2H, H^{a'}), 3.64 (m, 2H, H^a), 3.18 (ddd, *J* = 13.7, 13.7, 2.0 Hz, 1H, H^{6ax}), 2.04 (dd, *J* = 13.7, 3.4 Hz, 1H, H^{6eq}), 1.63 (m, 2H, H^{b'}), 1.55 (m, 2H, H^b), 1.39 (m, 2H, H^{c'}), 1.32 (m, 2H, H^c), 0.91 (t, *J* = 7.4 Hz, 3H, H^{d'}), 0.86 (t, *J* = 7.4 Hz, 3H, H^d). ¹³C{¹H} NMR (500 MHz, CDCl₃): δ/ppm = 207.4 (C^{CO2}), 206.8 (C^{CO1}), 158.3 (C^{D4}), 158.1 (C^{E4}), 153.9 (C^{B6}), 152.4 (C^{A6}), 149.4 (C^{B2}), 149.0 (C^{A2}), 145.9 (C^{C6}), 144.5 (C^{C2}), 143.8 (C^{C3}), 135.6 (C^{C4}), 134.9 (C^{A3}), 135.2 (C^{B4}), 134.8 (C^{A4}), 132.9 (C^{B3}), 132.3 (C^{D1}), 130.0 (C^{E1}), 129.7 (C^{E2}), 128.5 (C^{D2}), 124.1 (C^{C5}), 123.3 (C^{B5}), 122.7 (C^{A5}), 114.8 (C^{D3}), 114.6 (C^{E3}), 75.4 (C¹), 67.7 (C^{a'}), 67.5 (C^a), 53.3 (C⁴), 50.6 (C²), 46.7 (C³), 41.2 (C⁵), 38.8 (C⁶), 31.3 (C^{b'}), 31.2 (C^b), 19.3 (C^{c'}), 19.2 (C^c), 13.8 (C^{d'}), 13.7 (C^d). ESI-MS *m/z* 684.35 [M + H]⁺ (calc. 684.34). IR spectrum: see Figure S14. Found C 75.31, H 6.67, N 6.11; required for C₄₃H₄₅N₃O₅ C 75.52, H 6.63, N 6.14.

5. Conclusions

The preparation of terpyridines from the reactions of acetylpyridines with aromatic aldehydes and ammonia is an established synthetic method. Nevertheless, the reaction can give a variety of products. This paper provides another example of an "unexpected" product and a systematic survey of the products of such reactions. Although the one-pot synthesis of terpyridines is presented in the literature as an infallible synthetic method, there is ample precedent for the formation of a variety of alternative products. In particular, the assumption that the material precipitating from the reaction mixture is the desired terpyridine is not always correct. As these reactions are commonly used in the coordination chemistry community, this paper serves as a useful caveat. We are currently further investigating these reactions with varying length alkyloxy chains and will report on the constitution of the full reaction space in the future.

Supplementary Materials: The following are available online. Figures S1 and S2: Mass spectra of **5a** and **5c**; **Figure S3:** ¹³C{¹H} NMR spectra of **5a** and **5c**; Figures S4–S6: IR spectra of **5a**, **5c** and **6b**; **Figure S7:** Mass spectrum of **6b**; Figures S8–S10: NOESY, HMQC and HMBC spectra of **6b**; Figures S11 and S12: Mass spectra of **6a** and **6c**; Figures S3 and S4: IR spectra of **6a** and **6c**.

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Sample Availability: Samples of the compounds are available from the authors.



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