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Communication

4,4′-(Pyridin-4-ylmethylene)dibenzonitrile

Ben M. J. Lancaster, Alexander J. Nicholls and Ian R. Baxendale *

Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK; b.lancaster19@imperial.ac.uk (B.M.J.L.); alexander.j.nicholls@durham.ac.uk (A.J.N.)
* Correspondence: i.r.baxendale@durham.ac.uk

Abstract: This communication describes an unprecedented substitution cascade, in which 4-methylpyridine, following deprotonation with LDA, twice acts as a carbon nucleophile in an unusual S_NAr process, to form a novel triarylmethane structure. A proposed mechanism for this sequence is presented that is supported by single crystal X-ray analysis of the resulting product. We believe this unique transformation is of note as it highlights a neat and efficient entry as a single step to complex triarylmethane architectures containing both substituted phenyl and pyridyl aromatics.

Keywords: triarylmethanes; nucleophilic aromatic substitution; 4-picoline/4-methylpyridine; 4-fluorobenzonitrile

Citation: Lancaster, B.M.J.; Nicholls, A.J.; Baxendale, I.R. 4,4′-(Pyridin-4-ylmethylene) dibenzonitrile. *Molbank* **2021**, *2021*, M1302. https://doi.org/10.3390/M1302

Academic Editor: Rodrigo Abonia

Received: 19 November 2021
Accepted: 28 November 2021
Published: 30 November 2021

1. Introduction

C-Nucleophilic aromatic substitutions are of considerable importance to synthetic chemists as they allow the creation of molecular scaffolds, in this case forming high-energy C-C bonds in few stages [1,2]. Additionally, such processes can be part of more complex reaction cascades, resulting in the rapid construction of larger architectures that arise from a well-orchestrated and typically very step-efficient process [3]. The discovery of such pathways therefore allows chemists not only to access new chemical space, but moreover enables the design of novel structures in target-oriented synthesis programs.

2. Results and Discussion

A recent synthesis program in our laboratory concerned the activation of the C–H bonds of the methyl group of 4-methylpyridine (**1**), owing to its acidic behaviour in the presence of extremely strong bases. Our aim was to use such in situ generated nucleophiles to add to various aromatic nitriles, to generate, following work-up, the corresponding ketones, a reaction widely reported in the literature (Figure 1) [4–7]. However, the presence and positioning of a halogen-substituent (in particular, fluoro), combined with other electron withdrawing groups on an aromatic ring can arise to create an effective alternative electrophilic site. While this method is frequently utilised to form aromatic *C*-heteroatom bonds [8–11], the formation of C–C without any additional form of metal catalysis remains fairly unique.

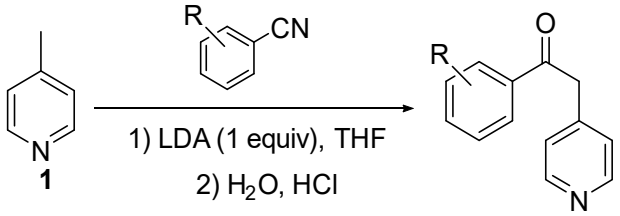

Figure 1. Synthesis of aryl pyridylmethyl ketone via addition to nitriles [4–7].

As encountered in our work, upon deprotonation of the methylpyridine (**1**) starting material, the formed carbanion can competitively attack instead the aryl electron deficient

centre of the 4-fluorobenzonitrile (**2**) acceptor (Figure 2). The instigation of *ipso* attack is promoted by the strong ability of the fluoro group to effectively polarise the associated carbon making it more susceptible to nucleophilic attack. Indeed, although the fluoride is a relatively good leaving group the associated C–F bond is strong, however, the desire for the system to regain aromaticity drives the fission of this bond, even at room temperature. The presence of the new group lowers the pK_A of the remaining alkyl protons, as the group is electron-withdrawing, hence a second deprotonation, instigated by the original 4-methylpyridine anion acting as the base, followed by a secondary S_NAr is likely more favourable than the original 4-methylpyridine anion attack on a new molecule of 4-fluorobenzonitrile (**2**), hence the tricyclic structure **3** is formed. No quaternary structures were observed, which provisionally indicates further nucleophilic attack is restricted due to steric hindrance.

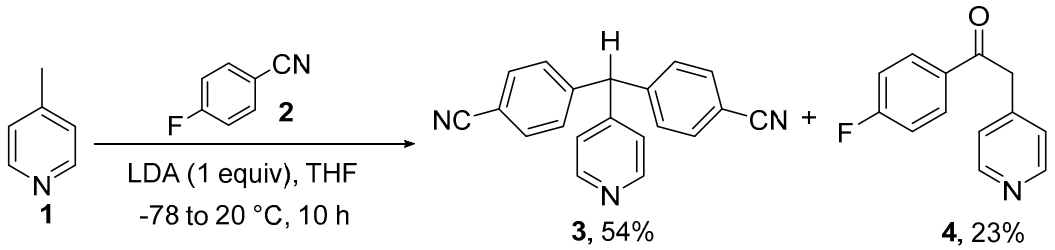

Figure 2. The synthetic scheme by which the title compound **3** was synthesised, alongside a by-product, **4** (percentage yield calculated from the amount of 4-fluorobenzonitrile (**2**) starting material, with **1** treated as being in excess) [7,12].

To fully account for this initially unexpected reaction outcome, we propose the following mechanistic rationale, based on understanding of electron-deficient fluorobenzenes (Figure 3) [13]. Deprotonation of the most-acidic proton of 4-methylpyridine is expected to generate the corresponding carbanion **1a** that allows a nucleophilic attack at the C–F bond of **2**. This intermediate eliminates F^- in order to re-gain aromaticity, forming intermediate **5**. As the pK_A of **5** is lower than that of **1**, a base more readily deprotonates **5**, forming **5a**. Compound **5a** enacts the comparable nucleophilic activity of **1a** on another unit of **2**, in order to generate the final intermediate that leads directly to **3** by eliminating F^-. At this point, the reaction progresses no further as to add another unit of **2** to the central carbon would assumingly generate an intermediate that is too sterically congested or as implied by the reaction of a related system needs additional catalysis to create the tetra-substituted centre [14]. The presence of two identical benzonitrile units removes any consideration of stereoselectivity and no products containing just one benzonitrile unit were detected in any significant quantities. As noted, the initially desired chemical product, **4**, [15] does indeed form albeit in low but significant yield, resulting from the addition of the carbanion **1a** to the nitrile, followed by hydrolysis during work-up. We note that a related condensation has been reported to occur between 2-pyridylacetonitrile and 4-fluorobenzonitrile in DMF in the presence of potassium tert-butoxide which supports the postulated condensation procedure outlined below [16].

Considering the stoichiometry of the reagents, product distribution and the estimated/measured pK_A's of the intermediates (**1** [17] 5.94, **3** and **5** [18] 5.58 $\pm$ 0.1) it was considered likely that the current reaction conditions were base limited. As such increasing the quantity of base was considered to be a useful approach to reaction optimisation. Ultimately this strategy proved beneficial with a 1.6 equivalent excess yielding the highest yield whilst limiting side reactions; a yield of 69% **3** and 24% **4**. Alternatively, a larger sacrificial excess of the 4-methylpyridine anion (**1a**) can be used to fully consume the 4-fluorobenzonitrile (**2**), in our hands using a 1.5 equivalent excess of **1a** gave the best results: 74% **3** and 21% **4** isolated.

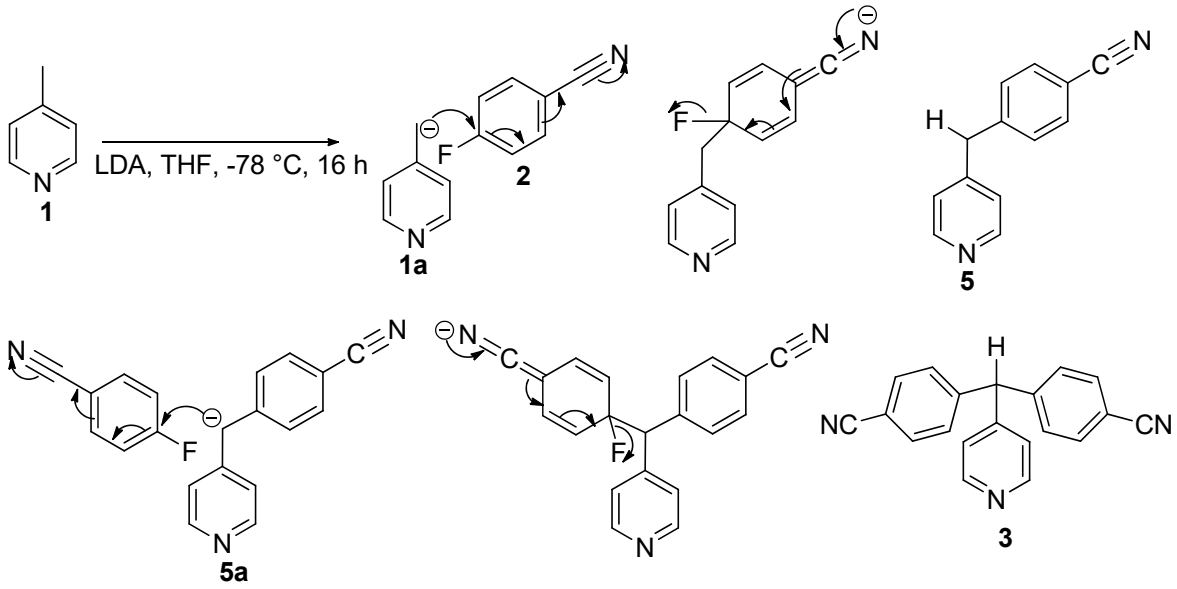

Figure 3. The proposed mechanism for the formation of the title compound **3**.

3. Materials and Methods

The initial synthesis of the title compound **3** from commercially available reagents was accomplished using the following procedure. Freshly distilled diisopropylamine (1.42 mL, 10.1 mmol) under an atmosphere of nitrogen (maintained throughout the entire synthesis) was dissolved in anhydrous THF (10 mL) and the solution was cooled to −78 °C (Note commercial lithium diisopropylamide solution 2 M in THF/heptane/ethylbenzene from Aldrich (St. Louis, MO, USA), part No. 361798 can also be used although yields were slightly lower 5–8%). *n*-BuLi (8.4 mL, 1.2 M in hexanes, 10 mmol) was then added dropwise. After 15 min, 4-methylpyridine (0.97 mL, 10 mmol) was added dropwise, resulting in a colour change to amber. After a further 30 min, a solution of 4-fluorobenzonitrile (1.21 g, 10 mmol) in anhydrous THF (5 mL) was added dropwise. The resulting solution was stirred at −78 °C for 1 h and then allowed to warm to 20 °C. After 10 h stirring at 20 °C, the reaction mixture was removed from the nitrogen atmosphere and then concentrated in vacuo, quenched with water (20 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo to yield a residue which was purified by column chromatography (30% hexanes/70% EtOAc) to give solid products **3** and **4** (0.49 g (23%)). Compound **3** was further recrystallised from dichloromethane to give off white crystals (0.80 g, 54% yield).

4,4′-(Pyridin-4-ylmethylene)dibenzonitrile (**3**) (see Supplementary Materials) $C_{20}H_{13}N_3$, M_r = 295.35 g mol^{-1}. off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 8.62–8.59 (2H, m, Aryl-*H*), 7.65 (4H, dm, *J* = 8.4 Hz, Aryl-*H*), 7.23–7.19 (4H, dm, *J* = 8.4 Hz, Aryl-*H*), 7.02–6.98 (2H, m, Aryl-*H*) and 5.62 (1H, s, $(Aryl)_3CH$). ^{13}C NMR (101 MHz, $CDCl_3$) 150.5 (*C*H), 149.7 (*C*), 146.0 (*C*), 132.7 (*C*H), 130.0 (*C*H), 124.2 (*C*H), 118.3 (*C*), 111.7 (*C*), 56.0 (*C*H). IR (neat) ν/cm^{-1} = 2228.6 (m, C≡N), 1604.2 (m), 1591.8 (s), 1500.0 (m), 1410.3 (s), 864.8 (m), 823.3 (s), 622.0 (s), 561.2 (s) and 537.9 (s). LC-MS: R_t = 1.73 min, *m*/*z* 296.7 [M + H$^+$]; HR-MS calculated for $C_{20}H_{14}N_3$ 296.1188, found: 296.1191 (Δ = 0.3 mDa). Crystal data for CCDC 2122916: monoclinic, space group P21/n (no. 14), at T = 120 K, a = 9.2835(6), b= 17.5421(11), c = 9.6559(6) Å, β = 90.090(3)°, V= 1572.5(2) Å3, Z = 4, Dc = 1.247 g cm^{-3}, 29095 reflections (3612 unique, Rint = 0.039), R1 = 0.044 on 2869 data with I > 2σ(I) and wR2 = 0.111 on all data (Figure 4).

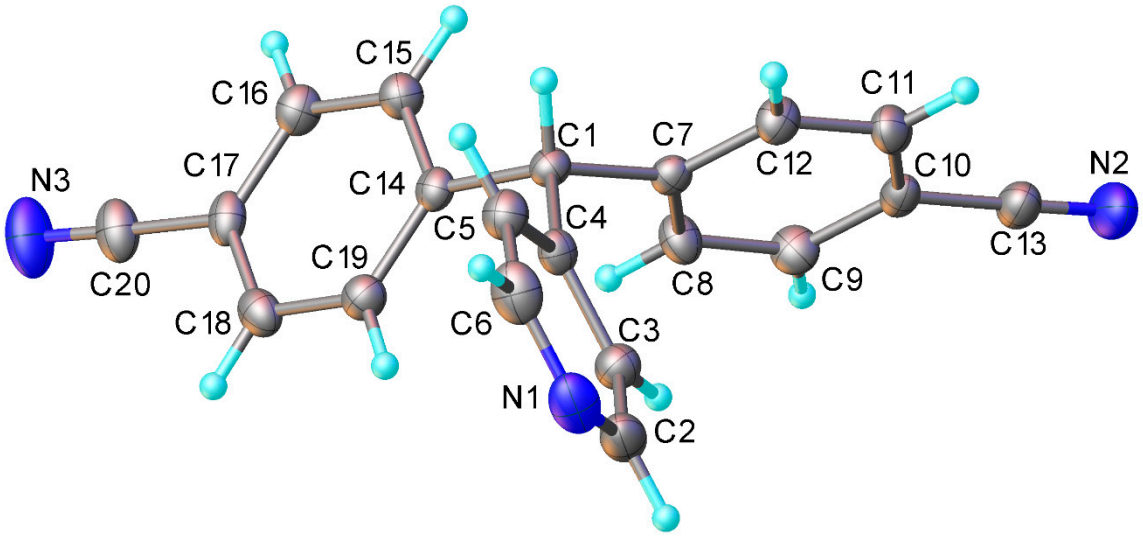

Figure 4. The X-ray structure recorded for compound **3**.

The improved synthesis condition for the title compound **3** employs the following procedure. Freshly distilled diisopropylamine (4.55 g, 45 mmol) dissolved in anhydrous THF (30 mL) under an atmosphere of nitrogen was cooled to −78 °C. To the solution was added *n*-BuLi (28.1 mL, 1.6 M in hexanes, 45 mmol) was then added dropwise. After 15 min, 4-methylpyridine (4.19 g, 45 mmol) in anhydrous THF (20 mL) was slowly (5 min) added. After complete addition the mixture was stirred for 15 min and a solution of 4-fluorobenzonitrile (3.63 g, 30 mmol) in anhydrous THF (20 mL) was added over 10 min. The resulting solution was stirred at −78 °C for 1 h and then allowed to warm to 20–25 °C (RT). After 10 h stirring at RT, the reaction mixture was concentrated in vacuo, quenched with water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo to yield a residue which was purified by column chromatography (30% hexanes/70% EtOAc) to give solid products **3** (3.27 g 74%) and **4** (1.36 g 21%). Compound **3** was recrystallised from dichloromethane to give cream crystals (2.88 g, 65% yield).

4. Conclusions

In conclusion, we have accomplished an efficient synthesis of a complex tricyclic system **3** by an S_NAr reaction. A mechanistic rationale accounting for this transformation is proposed. Due to the novelty of both this compound and the simplicity of the method, we believe such intriguing entities hold interest as they represent convenient routes to new triarylmethane compounds.

Supplementary Materials: The following are available online. NMR, IR and mass spectra as well as XRD data for the compounds **3** and **4**.

Author Contributions: The practical investigation and data analysis was accomplished by B.M.J.L. and A.J.N. The preparation of the original draft was performed by A.J.N. The funding acquisition, supervision as well as reviewing and editing the draft was completed by I.R.B. All authors have read and agreed to the published version of the manuscript.

Funding: We gratefully acknowledge financial support from Thomas Swan and Co. Ltd. during his PhD studies (A.J.N., RF030570).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Supporting data available (link to supporting data file submitted).

Acknowledgments: We furthermore are grateful to Andrei Batsanov (Durham University) for solving the X-ray crystal structure of compounds **3** and **4**.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the work, nor the decision to publish the results.

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