The insertion products of 2-picolyl lithium salt with benzonitrile and terephthalonitrile

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\textbf{Abstract} \\
Treatment of 2-picoline with Bu\textsuperscript{4}Li in THF affords its corresponding 2-picolyl lithium salt in a high yield. The insertion of benzonitrile into the Li–C bond of 2-picolyl lithium followed by acidic hydrolysis yields the corresponding \(\beta\)-pyridyl ketone (1), and diketone compounds (2) is obtained from 1 by intermolecular elimination of proton under the base condition. Similarly, the insertion of terephthalonitrile into 2-picolyl lithium leads to a 1,4-phenyl-linked pyridyl-azaalyl dilithium complex 4, followed by acidic hydrolysis yields corresponding 1,4-phenyl-linked dipryridylketone 3. The probable reaction pathway for the formation of 2 has been investigated. Compound 2 and 4 have been characterized by single-crystal X-ray crystallography. \\

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\textbf{1. Introduction} \\
Pyridine derivatives have become essential in many fields, such as coordination chemistry [1] and supramolecular chemistry [2]. The pyridine (C\textsubscript{5}H\textsubscript{5}N) ring framework is an important feature of a large amount of pharmaceutical [3] agrochemical [4] and natural products [5]. There are many different methodologies available to introduction of a pyridine ring into the construction of functionalized molecules. Of these various methods, one pathway drew our interest which was the lithiation of 2-picoline (2-methylpyridine) and subsequent electrophilic quenching [6]. Intriguingly, the lithiated 2-picoline salt exhibits a negative charge delocalized into the ring from carbanion to azaallyl and then relocalized onto the nitrogen atom through resonance (Chart. 1).\textsuperscript{7} \\

There have been a variety of studies on the alkali metal derivatives of \(\alpha\)-substituent picolines, however, most of them is focusing primarily on silylated derivatives [7,8]. These complexes were usually prepared by the insertion reaction of nitriles into an M–C bond of picolyl anion to form monomeric or dimeric pyridyl-substituted \(\alpha\)-azaalyl and enamido metal complexes. Recently, we reported the synthesis for a class of pyridyl substituted \(\alpha\)-azaallyl ligands and their corresponding metal complexes from lithiated 2-picoline followed by an insertion of nitriles [7a]. Furthermore, we have disclosed the insertion reactions of lithium silylquinolylamide salt with dimethylcyanamide afforded dimeric lithium quinolylguanidinates and transition metal Ti, Fe and Co quinolylguanidinates [9]. However, most insertion reactions were performed from the starting material of silylated picolyl lithium with nitriles to provide pyridyl azaallyl compound, in which the reaction involved a C–C coupling and 1,3-silyl group migration concomitantly. On the basis of this precedent reports, we are interested to explore a similar insertion approach using picolyl lithium instead of silylated picolyl lithium as a starting material reacted directly with nitriles. More recently, we have developed an efficient insertion reaction of pyridyl-/quinolyl-lithium with nitriles for preparing pyridyl-/quinolyl-ketone compounds and described their tautomeric equilibrium between enol, ketone and enaminone [10]. As an extension of our previous work, we herein describe the reaction of 2-picolyl lithium with benzonitrile and terephthalonitrile, respectively, and their inserted products followed by acidic hydrolysis to form the corresponding \(\beta\)-pyridyl ketone and diketone compounds.

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2. Experimental

2.1. General information

All air- and moisture-sensitive manipulations were carried out under dry N2 using standard Schlenk techniques. All reagents purchased from commercial sources were purified by standard techniques prior to use. Tetrahydrofuran and diethyl ether were dried by distilling from sodium/benzophenone. 1-Phenyl-2-(2-pyridinyl)-ethanoine (1) [10,12] was reported in published papers. NMR spectra were recorded on a Bruker AVANCE 600 (1H 600 MHz, 13C 150 MHz) at room temperature. The chemical shifts of 1H and 13C were referenced to TMS or residual solvent resonances. Elemental analyses were performed on a Vario EL III instrument.

2.2. Preparation of compounds 2–4

2.2.1. Compound 2

To a solution of 2-methylpyridine (1.40 g, 15 mmol) in 35 mL THF, BuLi (6.2 mL, 2.5 M solution in hexane, 15 mmol) was slowly added at 0 °C with stirring. The mixture was allowed to warm to room temperature for 4 h, after which benzonitrile (1.87 mL, 12.8 mmol) was added at 0 °C and then stirred for 6 h at room temperature. A sulfuric acid of 60% aqueous solution was then added dropwise until a PH of 1 was reached, and was stirred for 24 h to complete acidic hydrolysis, then neutralized with saturated aqueous KOH. The organic layer was extracted with CH2Cl2 (50 mL × 3), then dried over MgSO4 and concentrated by rotary evaporator. This compound was purified by reduced pressure distillation, resulting in yellow oil of 2 but slowly solidified. Yield: 2.31 g (79%). 1H NMR (600 MHz, CDCl3, 25 °C): δ = 8.47 (d, 2H, J1,H = 6.6 Hz, Ar–H), 8.41 (d, 2H, J1,H = 7.8 Hz, Ar–H), 8.04 (s, 2H, Ar–H), 7.85–7.12 (m, 10H, Ar–H), 6.37 (s, 2H, Ar–H) ppm. 13C NMR (150 MHz, CDCl3, 25 °C): δ = 197.96, 164.09, 158.66, 156.65, 149.96, 145.17, 138.90, 137.46, 137.35, 136.85, 134.18, 130.37, 130.15, 129.63, 129.08, 128.34, 126.03, 125.36, 122.78, 121.71, 119.93, 94.69 ppm. Anal. Calcd for C26H18N2O2: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.80; H, 4.54; N, 7.06.

2.2.2. Compound 3 and 4

Two preparation paths were available to compound 3. The method A for the synthesis of 3: To a solution of 2-methylpyridine (2.79 g, 30 mmol) in 60 mL THF, BuLi (18.0 mL, 2.5 M solution in hexane, 45 mmol) was slowly added at 0 °C with stirring. The mixture was allowed to warm to room temperature for 4 h, after which terephthalonitrile (1.63 g, 12.8 mmol) was added at 0 °C and then continued to stir for 48 h at room temperature, volatile materials were removed in vacuo, and dissolved in 10 mL of dry THF (Et2O = 1/1). Crystallization afforded the product 4 in the form of yellow block at ~30 °C. Yield: 8.15 g (79%). 1H NMR (600 MHz, CDCl3, 25 °C): δ = 8.36 (s, 2H, Py–H), 7.75 (d, 4H, J1,H = 7.8 Hz, Ar–H), 7.54 (s, 2H, Ar–H), 7.03 (t, 2H, J1,H = 7.8 Hz, Ar–H), 6.70 (d, 2H, J1,H = 7.2 Hz, Ar–H), 5.48 (s, 2H, –CH3), 3.56 (m, 5H, THF–CH2–H), 3.25 (m, 4H, Et3O–CH2–H), 1.40 (m, 8H, THF–CH2–H), 1.11 (6H, J1,H = 7.2 Hz, Et2O–CH3–H), 0.11 (s, 18H, Si(CH3)2–H) ppm. 13C NMR (150 MHz, CDCl3, 25 °C): δ = 160.44, 147.43, 135.68, 128.51, 128.34, 122.49, 117.74, 101.20, 67.83, 65.92, 25.81, 15.60 ppm. A sulfuric acid of 60% aqueous solution was then added dropwise to a solution of 4 in THF, until a PH of 1 was reached, and was stirred for 24 h to complete acidic hydrolysis, then neutralized with saturated aqueous KOH. The organic layer was extracted with CH2Cl2 (50 mL × 3), then dried over MgSO4 and concentrated by rotary evaporator. This compound was purified by reduced pressure distillation, resulting in yellow oil of 3 but slowly solidified. Yield: 3.80 g (65%). 1H NMR (600 MHz, CDCl3, 25 °C): δ = 8.47 (d, 2H, J1,H = 4.8 Hz, Py–H), 7.68 (s, 2H, Ar–H), 7.54 (m, 1H, J1,H = 7.5 Hz, Ar–H), 7.37 (d, 3H, J1,H = 4.8 Hz, Ar–H), 7.06 (d, 2H, J1,H = 8.4 Hz, Ar–H), 6.89 (m, 2H, J1,H = 6.0 Hz, Ar–H), 4.70 (s, 4H, –CH2–H) ppm. 13C NMR (150 MHz, CDCl3, 25 °C): δ = 163.81, 158.62, 149.75,144.60, 137.52, 129.06, 125.71, 122.12, 121.84, 119.34, 96.16, 48.71 ppm. Anal. Calcd for C27H23N2O2: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.04; H, 4.92; N, 8.67.

2.3. X-ray crystallography

X-ray diffraction data were collected on a Bruker D8 Venture CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods [13,14]. All non-H atoms were refined anisotropically and the H atoms were included in calculated positions [13,14]. CCDC 1423198 (2) and CCDC 1562507 (4) contains the supplementary crystallographic data which can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. Crystallographic data for compounds 2 and 4 are summarized in Table 1.

3. Results and discussion

3.1. Synthesis and possible mechanism of compounds 1–4

The general synthesis route for the compounds of β-pyridyl ketone and diketone 1–4 presented in this paper is illustrated in Scheme 1. The starting material 2-picolyllithium was prepared by lithiation of 2-picoline with 1.2 equiv. of BuLi in THF solvent at 0 °C. Compound 1 and 2 were isolated in a good yield by the reaction of 2-picolyllithium with an equimolar amount benzonitrile in situ, followed by acidic hydrolysis and neutralized with saturated solution of KOH. Compound β-pyridyl ketone 1 has been previously reported by our group [10]. Compound 3 exists in a tautomeric mixture of enol and ketone as a yellow oil, in which enol form is dominant in solution or pure material. A similar preparation to 1, while neutralized acid with excess KOH solution or treatment of 1 with excess saturated KOH aqueous in THF afforded β-pyridyl diketone compound 2. Compound 2 was isolated as yellow crystals with yield of 42%. Crystals of 2 suitable for X-ray diffraction study were grown from dichloromethane at ~30 °C for 3 days.
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