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

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ABSTRACT

Treatment of 2-picoline with Bu^nLi 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 β-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 dipyridylketone **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.

1. Introduction

Pyridine derivatives have become essential in many fields, such as coordination chemistry [1] and supramolecular chemistry [2]. The pyridine (C_5H_5N) 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).[7]

There have been a variety of studies on the alkali metal derivatives of α-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 1-azaallyl and enamido metal complexes. Recently, we reported the synthesis for a class of pyridyl substituted 1-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 pyridlyl 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 β-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 N_2 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)-ethanone (**1**) [10,12] was reported in published papers. NMR spectra were recorded on a Bruker AVANCE 600 (^{1}H 600 MHz, ^{13}C 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, ^{n}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, 15 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 solution until a PH of 14 was reached. The organic layer was extracted with CH_2Cl_2 (50 mL × 3), then dried over $MgSO_4$ 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%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.47 (d, 2H, $J_{H\text{-}H}$ = 6.6 Hz, Ar—H), 8.41 (d, 2H, $J_{H\text{-}H}$ = 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. ^{13}C NMR (150 MHz, $CDCl_3$, 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, 122.71, 119.93, 94.69 ppm. Anal. Calcd for $C_{26}H_{18}N_2O_2$: 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, ^{n}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 (1.92 g, 15 mmol) was added at 0 °C and then stirred for 48 h at room temperature. A sulfuric acid of 60% aqueous solution was then added to the above mixture 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 CH_2Cl_2 (50 mL × 3), then dried over $MgSO_4$ and concentrated by rotary evaporator. This was recrystallized from (CH_2Cl_2/Hexane = 1/1) then purified by chromatography (petroleum ether/ethyl acetate = 1/1) to afford a yellow powder **3**. Yield: 0.47 g (8%).

The method B for the synthesis of **3** and **4**: To a solution of 2-methylpyridine (2.79 g, 30 mmol) in 60 mL THF, ^{n}BuLi (12.0 mL, 2.5 M solution in hexane, 30 mmol) was slowly added at 0 °C with stirring. The mixture was allowed to warm to room temperature for 12 h, after which trimethyl chlorosilane (4.94 mL, 39 mmol) was added at 0 °C and then stirred for 24 h at room temperature. This silyl-substituted compound was purified by reduced pressure distillation, Bp 62 °C at 3 mbar. Yield: 4.21 g (85%). Then dissolved this silyl-substituted compound in 60 mL (THF/Et_2O = 1/1), ^{n}BuLi (10.2 mL, 2.5 M solution in hexane, 25.5 mmol) was slowly added at 0 °C with stirring. The mixture was allowed to warm to room temperature and stirred for 12 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 vacuuo*, and dissolved in 10 mL of dry (THF/Et_2O = 1/1). Crystallization afforded the product **4** in the form of yellow block at −30 °C. Yield: 8.15 g (79%). ^{1}H NMR (600 MHz, C_6D_6, 25 °C): δ = 8.36 (s, 2H, Py-H), 7.75 (d, 4H, $J_{H\text{-}H}$ = 7.8 Hz, Ar—H), 7.54 (s, 2H, Ar—H),7.03 (t, 2H, $J_{H\text{-}H}$ = 7.8 Hz, Ar—H), 6.70 (d, 2H, $J_{H\text{-}H}$ = 7.2 Hz, Ar—H), 5.48 (s, 2H, =CH), 3.56 (m, 8H, THF—CH_2—H), 3.25 (m, 4H, Et_2O—CH_2—H), 1.40 (m, 8H, THF—CH_2—H), 1.11 (6H, $J_{H\text{-}H}$ = 7.2 Hz, Et_2O—CH_3—H), 0.11 (s, 18H, $Si(CH_3)_3$—H) ppm. ^{13}C NMR (150 MHz, C_6D_6, 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 CH_2Cl_2 (50 mL × 3), then dried over $MgSO_4$ and concentrated by rotary evaporator. This was recrystallized from (CH_2Cl_2/Hexane = 1/1) then purified by chromatography (petroleum ether/ethyl acetate = 1/1) to afford a yellow powder **3**. Yield: 3.80 g (65%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.47 (d, 2H, $J_{H\text{-}H}$ = 4.8 Hz, Py-H), 7.68 (s, 2H, Ar—H), 7.54 (m, 1H, $J_{H\text{-}H}$ = 7.5 Hz, Ar—H), 7.37 (d, 3H, $J_{H\text{-}H}$ = 4.8 Hz, Ar—H), 7.06 (d, 2H, $J_{H\text{-}H}$ = 8.4 Hz, Ar—H), 6.89 (m, 2H, $J_{H\text{-}H}$ = 6.0 Hz, Ar—H), 4.70 (s, 4H, —CH_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 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 $C_{26}H_{18}N_2O_2$: 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 = 0.71,073 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-picolyl lithium was prepared by lithiation of 2-picoline with 1.2 equiv. of Bu^{n}Li in THF solvent at 0 °C. Compound **1** and **2** were isolated in a good yield by the reaction of 2-picolyl lithium 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 **1** 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.