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SHORT COMMUNICATIONS

Effective Synthetic Approach to 4-Arylpyridine-2,6-dicarboxylic Acids

O. V. Shabunina[a], D. N. Kozhevnikov[b], D. S. Kopchuk[a,c], G. V. Zyryanov[a,c,*], A. I. Suvorova[a], V. L. Rusinov[a,c], and O. N. Chupakhin[a,c]

[a] *Yeltsin Ural Federal University, Yekaterinburg, 620002 Russia*

[b] *Frishberg Institute of Applied Chemistry and Certification, Yekaterinburg, 620016 Russia*

[c] *Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, Yekaterinburg, 620990 Russia*

**e-mail: gvzyryanov@gmail.com*

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Abstract—A convenient synthetic route to 4-arylpyridine-2,6-dicarboxylic acid has been proposed on the basis of substituted benzaldehydes according to the Kröhnke method, followed by oxidation of methyl group.

Keywords: pyridine-2,6-dicarboxylic acids, Kröhnke method, heterocyclization, oxidation

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Pyridine-2,6-dicarboxylic acid derivatives are of interest as important building blocks for the design of oligopyridine ligands [1–3], lanthanide complexes for various purpose [4, 5], and chelating agents for rare earth cations [6]. Furthermore, some pyridine-2,6-dicarboxylic acids exhibit biological activity, e.g., as New Delhi metallo-β-lactamase-1 inhibitors [7].

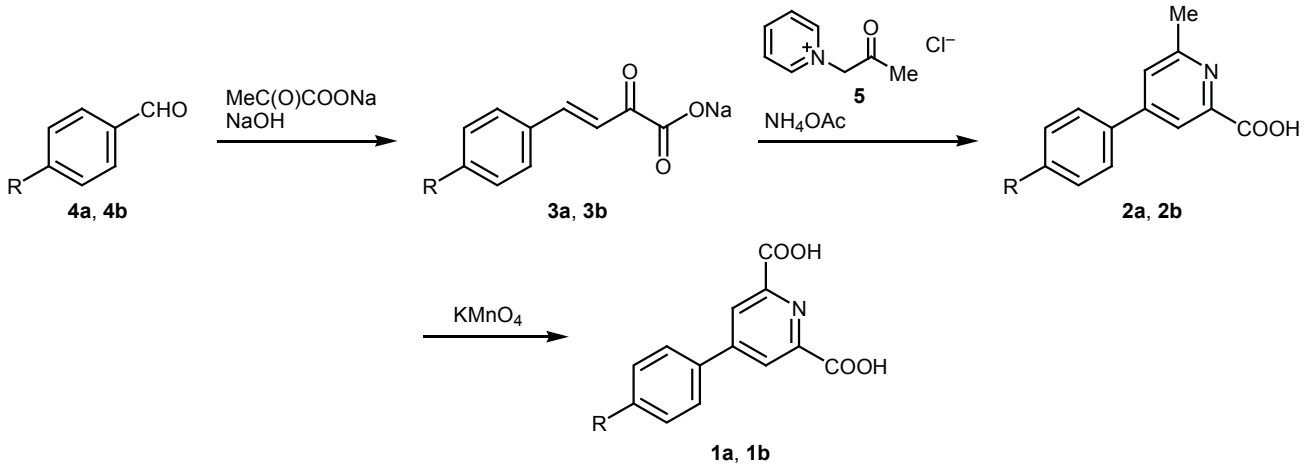
The present work was aimed at synthesizing 4-arylpyridine-2,6-dicarboxylic acids. The known methods for the preparation of such compounds include oxidation of the two furan-2-yl substituents in the 2,6-positions of pyridine [1, 8, 9] and oxidation of 2,6-dimethylpyridines [10, 11]. Furthermore, an aromatic or heteroaromatic substituent can be introduced via various cross-coupling reactions with 4-halopyridines [4, 12–15] or pyridin-4-ylboronic acids [16]. 4-Arylpyridine-2,6-dicarboxylic acid esters can be synthesized by the Kröhnke heterocyclization [17] or related reactions [18, 19], as well as by other methods [20]. Cross-coupling reactions have also been extensively used for this purpose [21]. In addition, syntheses of 4-arylpyridine-2,6-dicarboxylic acid esters from pyrylium tetrafluoroborate [10, 22] and 3,4-dihydro-2*H*-pyran derivatives [23, 24], through 1,2,4-triazine analogs with subsequent replacement of the carboxy group on C^5 [25], and construction of a heterocycle at C^4 as a result of click reaction [26, 27] have been reported.

In this work we obtained 4-aryl-6-methylpyridine-2-carboxylic acids **2** as precursors to 4-arylpyridine-2,6-dicarboxylic acids **1** according to the Kröhnke method. Intermediate chalcones **3** were synthesized from aldehydes **4** and sodium pyruvate following a modified procedure [28] (Scheme 1). The heterocyclization stage was carried out in aqueous medium, and the procedure was different from that described previously [29]. In the final step, permanganate oxidation of the 6-methyl group in **2** in aqueous medium afforded target dicarboxylic acids **1**.

The structure of compounds **1–3** was confirmed by ^{1}H NMR and mass spectra and elemental analyses. The ^{1}H NMR spectra of **3** characteristically showed doublet signals of the ethylene fragment with a coupling constant corresponding to *trans* configuration of the double bond. In the ^{1}H NMR spectra of **2**, protons of the 6-methyl group resonated in the region δ 2.59–2.60 ppm, and signals of protons of the pyridine rings appeared as two doublets. The spectra of diacids **1** lacked methyl proton signal, and protons of the pyridine ring resonated as a singlet.

In summary, we have proposed an efficient synthetic approach to 4-arylpyridine-2,6-dicarboxylic acids

Scheme 1.



R = Cl (**a**), MeO (**b**).

which may be interesting from the viewpoint of their practical application in various fields.

Sodium (*E*)-4-aryl-2-oxobut-3-enoates 3a and 3b (*general procedure*). Aldehyde **4a** or **4b** (50 mmol) was dissolved in 50 mL of ethanol, a solution of sodium pyruvate (6.05 g, 55 mmol) in water (50 mL) was added, the mixture was stirred on cooling with an ice bath, and a 10% solution of sodium hydroxide (50 mL) was slowly added at such a rate that the temperature did not exceed 5–10°C. The mixture was then stirred for 1 h more, and the precipitate was filtered off and washed with a small amount of ethanol.

Sodium 4-(4-chlorophenyl)-2-oxobut-3-enoate (3a). Yield 10.79 g (46.5 mmol, 93%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.85 d (1H, CH=CH, J = 15.9 Hz), 7.39 m (2H, C_6H_4), 7.40 d (1H, CH=CH, J = 15.9 Hz), 7.65 m (2H, C_6H_4). Mass spectrum: m/z 209.00 (I_{rel} 100%) [M – Na]$^-$. $C_{10}H_6ClO_3$. Calculated: M – Na 209.00.

Sodium 4-(4-methoxyphenyl)-2-oxobut-3-enoate (3b). Yield 10.94 g (48 mmol, 96%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.80 s (3H, OMe), 6.68 d (1H, CH=CH, J = 15.9 Hz), 6.94 m (2H, C_6H_4), 7.41 (1H, CH=CH, J = 15.9 Hz), 7.57 m (2H, C_6H_4). Mass spectrum: m/z 205.05 (I_{rel} 100%): [M – Na]$^-$. $C_{11}H_9O_4$. Calculated: M – Na 205.05.

4-Aryl-6-methylpyridine-2-carboxylic acids 2a and 2b (*general procedure*). A solution of sodium 4-aryl-2-oxobut-3-enoate **3a** or **3b** (50 mmol), 1-(2-oxopropyl)pyridinium chloride (**5**, 14.46 g, 55 mmol), and ammonium acetate (4.62 g, 60 mmol) in 100 mL of water was refluxed for 2 h. The mixture was cooled to room temperature, and the precipitate was filtered off and washed with water.

4-(4-Chlorophenyl)-6-methylpyridine-2-carboxylic acid (2a). Yield 10.62 g (43 mmol, 86%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.59 s (3H, Me), 7.53 m (2H, C_6H_4), 7.60 d (1H, 5-H, J = 1.2 Hz), 7.75 m (2H, C_6H_4), 8.03 d (1H, 3-H, J = 1.2 Hz). Mass spectrum: m/z 246.03 (I_{rel} 100%) [M – H]$^-$. $C_{13}H_9ClNO_2$. Calculated: M – H 246.03.

4-(4-Methoxyphenyl)-6-methylpyridine-2-carboxylic acid (2b). Yield 11.06 g (45.5 mmol, 91%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.60 s (3H, Me), 3.80 s (3H, OMe), 7.50 m (2H, C_6H_4), 7.60 d (1H, 5-H, J = 1.2 Hz), 7.75 m (2H, C_6H_4), 8.04 d (1H, 3-H, J = 1.2 Hz). Mass spectrum: m/z 242.08 (I_{rel} 100%) [M – H]$^-$. $C_{14}H_{12}NO_3$. Calculated: M –H 242.08.

4-Arylpyridine-2,6-dicarboxylic acids 1a and 1b (*general procedure*). A suspesion of acid **2a** or **2b** (30 mmol) in water (200 mL) was heated to 90°C, and potassium permanganate (11 g, 69.7 mmol) was added in 1.1-g (6.97-mmol) portions with stirring. Each subsequent portion was added only after decoloration of the mixture. The precipitate was filtered off and washed with hot water. The filtrate was combined with the washings and acidified to slightly acidic reaction with concentrated aqueous HCl. The precipitate was filtered off and recrystallized from acetic acid.

4-(4-Chlorophenyl)pyridine-2,6-dicarboxylic acid (1a). Yield 5.57 g (20.1 mmol, 67%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.55 m (2H, C_6H_4), 7.85 m (2H, C_6H_4), 8.45 s (2H, 3-H, 5-H). Found, %: C 56.11; H 3.02; N 5.22. $C_{13}H_8ClNO_4$. Calculated, %: C 56.23; H 2.90; N 5.04.

4-(4-Methoxyphenyl)pyridine-2,6-dicarboxylic acid (1b). Yield 3.93 g (14.4 mmol, 48%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.80 s (3H, OMe), 7.05 m (2H, C_6H_4), 7.75 m (2H, C_6H_4), 8.43 s (2H, 3-H, 5-H). Found, %: C 61.67; H 3.89; N 5.01. $C_{14}H_{11}NO_5$. Calculated, %: C 61.54; H 4.06; N 5.13.

The ^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 MHz using tetramethylsilane as internal standard. The mass spectra (electrospray ionization) were recorded on a Bruker Daltonics MicrOTOF-Q II instrument (Bremen, Germany). Elemental analysis was performed with a Perkin Elmer 2400 Series II CHN analyzer. Pyridinium salt **5** was prepared according to the procedure described in [30].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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