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Chinese Chemical Letters 20 (2009) 771–774
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

A novel synthesis of 5-aryl-3-cyano-2-pyridones by using vinamidinium salts

Xue Hui Zhang, Wu Zhong, Xing Zhou Li, Song Li *

Beijing Institute of Pharmacology and Toxicology, Beijing 100850, China

Received 15 December 2008

Abstract

A variety of vinamidinium salts were condensated with cyanoacetamide in refluxing methanol that contained sodium methoxide to produce 5-aryl-3-cyano-2-pyridones in good yield. Simple experimental conditions were used to prepare ten different 5-aryl-3-cyano-2-pyridones, four of which are new compounds.

Keywords: 5-Aryl-3-cyano-2-pyridones; Vinamidinium salts; Cyclization

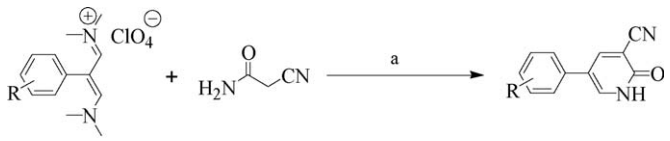
The 2-pyridones are a class of important heteroaromatic compounds. 5-Aryl-3-cyano-2-pyridones have been prepared by the cyclization of cyanoacetamide condensated with 2-aryl-3-dimethylamino-2-propenals [1,2]. The vinamidinium salts undergo condensation reactions, similar to malonaldehyde derivatives, with bifunctional nucleophiles to form heterocycles [3]. While the vinamidinium salts have been used to prepare many different heterocycles [3] including isoxazoles, pyrazoles, pyrimidines, pyrroles [4] and thiophenes [5,6], they have not yet been used to prepare 5-aryl-3-cyano-2-pyridones. In this report, an application of 2-arylvinamidinium salts to prepare 5-aryl-3-cyano-2-pyridones is presented.

The vinamidinium salts (**1a–j**) used in this study were prepared by the standard Vilsmeier–Haack reaction from the appropriate aryl acetic acid [4,7]. As shown in Scheme 1, the 1.0 equiv 2-arylvinamidinium salts (**1a–j**) were condensed with 1.0 equiv cyanoacetamide in refluxing methanol that contained sodium methoxide to give the desired 5-aryl-3-cyano-2-pyridones (**3a–j**). In general [8], 2.0 equiv sodium methoxide was sufficient to give good result. But in the case of preparing 3-cyano-5-(4-hydroxyphenyl)-2-pyridones (**3c**), 3.0 equiv sodium methoxide was required, because the hydroxy in the starting material 2-(4-hydroxyphenyl)vinamidinium salt (**1c**) consumed 1.0 equiv sodium methoxide. The most part of the reactions were rather clean and proceeded in good yield. The conditions and results were listed in Table 1.

The products, 5-aryl-3-cyano-2-pyridones, were all analyzed by ^{1}H NMR, EI-MS and HREI spectroscopic methods [11]. The 5-aryl-3-cyano-2-pyridones **3b**, **3e**, **3f** and **3g** are new compounds. The compounds **3a** [2], **3c** [9], **3d** [9], **3h** [10] and **3i** [10] are known compounds and their spectroscopic data have not been reported. In the reported ^{1}H NMR

* Corresponding author.
E-mail address: lis@nic.bmi.ac.cn (S. Li).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.02.016



(a) $NaOCH_3$, CH_3OH, reflux; HCl, H_2O.

Scheme 1. Preparation of 5-aryl-3-cyano-2-pyridones (a) $NaOCH_3$, CH_3OH, reflux; HCl, H_2O.

Table 1
Reaction conditions and results.

Entry	R	Time (h)	Crude Yield (%)
3a	H	4.0	90
3b	4-Methyl	4.5	83
3c	4-Hydroxy	4.5	85
3d	4-Methoxy	4.5	87
3e	4-Ethoxy	4.5	87
3f	4-(Benzyloxy)	4.0	90
3g	2-Fluoro	4.0	88
3h	2-Chloro	3.5	91
3i	4-Chloro	3.5	93
3j	4-Nitro	3.0	95

spectroscopic data of **3j**, the peak *(* 3.4 of HDO in DMSO-d_6 was mistakenly taken for the signal of NH proton by author [1]. The experimental HRMS data matched the calculated data [11].

The geometry of the 5-aryl-3-cyano-2-pyridone ring was established by the coupled H-4 and H-6 NMR peaks *(* 8.74 (d, 1H, ^4J = 2.8 Hz) and 8.38 (d, 1H, ^4J = 2.8 Hz), and the signal *(* 13.12 (brs, 1H) of the active proton, respectively for

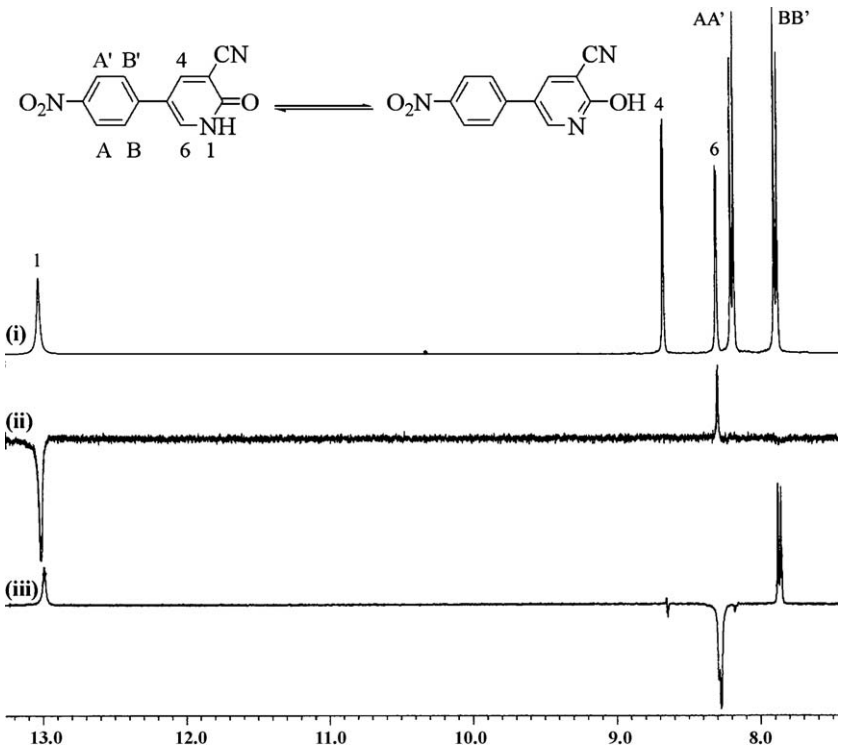


Fig. 1. Tautomerism, ^{1}H NMR and NOE difference spectrometry experiment for compound **3j**.

compound **3j** [11] in DMSO-d_6, as shown in Fig. 1. Because of the tautomerism of 2-pyridones in solution, there may be two tautomeric forms: 2-pyridone and 2-hydroxypyridine, and the tautomeric equilibrium is dependent on the polarity of the solvent [12]. In the NOE difference experiment for **3j** in DMSO-d_6 (Fig. 1), (**ii**) shows enhancement of the H-6 on irradiation of the active proton, and (**iii**) shows enhancement of both the active proton and the H-BB' on irradiation of the H-6. The result indicated that the active proton was on the N-1, and the formation of 2-pyridone is predominant in DMSO-d_6. The conclusion investigated by NOE difference spectrometry is in agreement with the early research by UV–vis spectroscopic method [12].

In summary, a variety of vinamidinium salts were condensated with cyanoacetamide in refluxing methanol that contained sodium methoxide to produce 5-aryl-3-cyano-2-pyridones with good yield and in simple experimental process. The predominant formation in DMSO-d_6 was determined by using ^{1}H NMR and NOE difference spectrometry.

Acknowledgments

This work was supported by the National Basic Research Program of China (No. 2004CB518908) and the National High Technology Research and Development Program of China (No. 2006AA020601).

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[8] *General procedure*: To a dry 50-mL, two-necked flask equipped with a reflux condenser and drying tube, was added 20 mL absolute methanol and sodium(46 mg, 2 mmol). The mixture was stirred for 5 min. To the solution, cyanoacetamide (84 mg, 1 mmol) and vinamidinium salt (1 mmol) were introduced. The mixture was refluxed for several hours during which time a solid separated, cooled to room temperature. The mixture was added 15 mL water, acidified with 1 mol/L HCl. The solid crude product was filtered, washed with water and hexane, and then recrystilized in methanol to obtain purified product.
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[11] 3-Cyano-5-phenyl-2-pyridone (**3a**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.90 (brs, 1H), 8.59 (d, 1H, J = 2.8 Hz), 8.14 (d, 1H, J = 2.8 Hz), 7.64 (m, 2H), 7.43 (m, 2H), 7.34 (m, 1H); EI-MS (*m/z*, %): 196 [M^+, 100], 168 [19.4], 154 [2.3], 140 [18.8]; HREI calcd. for $C_{12}H_8N_2O$ 196.0637, found 196.0639;
3-Cyano-5-p-tolyl-2-pyridone (**3b**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.85 (brs, 1H), 8.56 (d, 1H, J = 2.8 Hz), 8.09 (d, 1H, J = 2.8 Hz), 7.52 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.0 Hz), 2.32 (s, 3H); EI-MS (*m/z*, %): 210 [M^+, 100], 195 [3.6], 182 [8.2], 181 [11.6], 154 [7.4], 140 [5.2], 91 [3.0], 77 [2.5]; HREI calcd. for $C_{13}H_{10}N_2O$ 210.0793, found 210.0796; IR (KBr): ν = 2234 (CN), 1655 (C═O), 1614, 1557, 1516 cm^{-1};
3-Cyano-5-(4-hydroxyphenyl)-2-pyridone (**3c**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.73 (brs, 1H), 9.56 (s, 1H), 8.46 (d, 1H, J = 2.8 Hz), 7.97 (d, 1H, J = 2.8 Hz), 7.42 (d, 2H, J = 8.7 Hz), 6.80 (d, 2H, J = 8.7 Hz); EI-MS (*m/z*, %): 212 [M^+, 100], 195 [3.0], 184 [7.1], 156 [10.6], 140 [3.73], 133 [7.7]; HREI calcd. for $C_{12}H_8N_2O_2$ 212.0586, found 212.0587;
3-Cyano-5-(4-methoxyphenyl)-2-pyridone (**3d**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.77 (brs, 1H), 8.51 (d, 1H, J = 2.8 Hz), 8.04 (d, 1H, J = 2.8 Hz), 7.55 (d, 2H, J = 8.9 Hz), 6.98 (d, 2H, J = 8.9 Hz), 3.78 (s, 3H); EI-MS (*m/z*, %): 226 [M^+, 100], 211 [39.8], 195 [1.6], 183 [11.0], 155 [11.0], 140 [3.3], 91 [2.0], 77 [3.1]; HREI calcd. for $C_{13}H_{10}N_2O_2$ 226.0742, found 226.0744;
3-Cyano-5-(4-ethoxyphenyl)-2-pyridone (**3e**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.77 (brs, 1H), 8.51 (d, 1H, J = 2.8 Hz), 8.03 (d, 1H, J = 2.8 Hz), 7.54 (d, 2H, J = 8.7 Hz), 6.96 (d, 2H, J = 8.7 Hz), 4.04 (q, 2H, J = 7.0 Hz), 1.33 (t, 3H, J = 7.0 Hz); EI-MS (*m/z*, %): 240 [M^+, 73], 212 [100], 195 [3.9], 184 [7.8], 156 [8.0], 140 [3.9], 77 [2.53]; HREI calcd. for $C_{14}H_{12}N_2O_2$ 240.0899, found 240.0894; IR (KBr): ν = 2234 (CN), 1652 (C═O), 1615, 1558, 1517 cm^{-1};
3-Cyano-5-(4-(benzyloxy)phenyl)-2-pyridone (**3f**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.78 (brs, 1H), 8.51 (d, 1H, J = 2.8 Hz), 8.03 (d, 1H, J = 2.8 Hz), 7.55 (d, 2H, J = 8.7 Hz), 7.31∼7.47 (m, 5H), 7.06 (d, 2H, J = 8.7 Hz), 5.14 (s, 2H); EI-MS (*m/z*, %): 302 [M^+, 9.5], 224 [0.7], 212 [1.5], 155 [0.7], 91 [100], 77 [0.7], 65 [5.3]; HREI calcd. for $C_{19}H_{14}N_2O_2$ 302.1055, fou nd 302.1059; IR (KBr): ν = 2230 (CN), 1666 (C═O), 1611, 1557, 1516 cm^{-1};
3-Cyano-5-(2-fluorophenyl)-2-pyridone (**3g**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.90 (brs, 1H), 8.41 (d, 1H, J = 1.7 Hz), 8.02 (d, 1H, J;= 1.7 Hz), 7.55∼7.59 (m, 1H), 7.38∼7.44 (m, 1H), 7.26∼7.33 (m, 2H); EI-MS (*m/z*, %): 214 [M^+, 100], 195 [2.0], 186 [29.4], 158 [19.6], 140

[2.2], 135 [9.8]; HREI calcd. for $C_{12}H_7FN_2O$ 214.0542, found 214.0544; IR (KBr): ν = 2230 (CN), 1697 (C═O), 1649, 1607, 1551;cm^{-1};
3-Cyano-5-(2-chlorophenyl)-2-pyridone (**3h**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.92 (brs, 1H), 8.34 (d, 1H, J = 2.6 Hz), 7.94 (d, 1H, J = 2.6 Hz), 7.56∼7.59 (m, 1H), 7.48∼7.50 (m, 1H), 7.41∼7.43 (m, 2H); EI-MS (m/z, %): 232 [M^++2, 30], 230 [M^+, 100], 214 [16.0], 202 [18.0], 195 [19.2], 174 [4.1], 167 [5.7], 151 [4.5], 140 [27.3]; HREI calcd. for $C_{12}H_7ClN_2O$ 230.0247, found 230.0253;
3-Cyano-5-(4-chlorophenyl)-2-pyridone (**3i**): 1H NMR (400 MHz, DMSO-d6, δ ppm): 12.90 (brs, 1H), 8.59 (d, 1H, J = 2.7 Hz), 8.16 (d, 1H, J = 2.7 Hz), 7.67 (d, 2H, J =;8.5 Hz), 7.47 (d, 2H, J = 8.5 Hz); EI-MS (m/z, %): 232 [M^++2, 30], 230 [M^+, 100], 202 [15.2], 195 [7.3], 174 [5.2], 174 [5.2], 167 [5.2], 151 [8.3], 140 [20.9]; HREI calcd. for $C_{12}H_7ClN_2O$ 230.0247, found 230.0244;
3-Cyano-5-(4-nitrophenyl)-2-pyridone (3j): 1H NMR (400 MHz,;1; DMSO-d6, δ ppm): 13.12 (brs, 1H), 8.74 (d, 1H, J = 2.8 Hz), 8.38 (d, 1H, J = 2.8 Hz), 8.25 (d, 2H, J = 9.0 Hz), 7.95 (d, 2H, J = 9.0 Hz); EI-MS (m/z, %): 241 [M^+, 100], 211 [15.7], 195 [6.1], 167 [5.7], 140 [44.6], 130 [15.0], 91 [6.3]; HREI calcd. for $C_{12}H_7N_3O_3$ 241.0487, found 241.0483.

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