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Preferential Reactivity of Pyridylmagnesiumchloride with N,N-Dialkyl Arylamides over Carbonitriles: Synthesis of 2-(Aroyl) Pyridines

G. Venkateswara Rao, B. Narayana Swamy, P. Hareesh Kumar, and G. Chandrasekara Reddy
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Abstract: Reaction of 2-pyridylmagnesium chlorides with *N*,*N*-dialkyl arylamides afford exclusively 2-(aroyl) pyridines in high yields and purity without the formation of any tertiary alcohol. This method employs easily available raw materials and avoids the use of hazardous lithium reagents and cryogenic conditions. Further, preferential reactivity of this Grignard reagent with *N*,*N*-dialkyl arylamides over its carbonitrile counterparts offers a variety of 2-(aroyl) pyridines including the ones containing carbonitrile groups on the aryl ring.

Keywords: Aroylpyridines, dialkyl arylamides, Grignard reagent, preferential reaction, pyridylmagnesium chloride

2-(Aroyl) pyridines have received wide attention as precursors in the synthesis of a variety of active pharmaceutical ingredients such as acrivastine,[1] carbinoxamine,[2] doxylamine,[3] pipradral,[4] pirmenol,[5] rimiterol,[6] triprolidine,[7] zimeldine,[8] and so forth. The generally accepted method for introducing acyl groups into aromatic and heteroaromatic rings is direct Friedel–Crafts acylation or by reacting metallated aryl compounds with reagents such as *N*,*N*-dimethylamides,[9] *N*-methoxy-*N*-methylamides (Weinreb amides),[10] *O*-alkyl oximes

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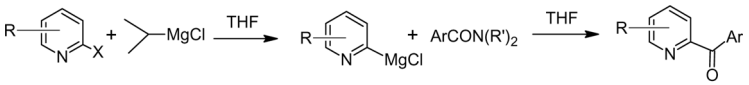
of aldehydes,[11] *N*-(ethoxymethylene)aniline,[12] acid chlorides,[13] nitriles,[14] and aroyl cyanides.[15]

However, the inertness of pyridine to electrophillic substitution and its capacity to form complexes with Lewis acids, which further decreases electron density on the ring, make the acylation impossible without prior structural modifications. Even after structural modification, acylation takes place only on the third position of the ring.[16] Hence, there are many indirect ways to make 2-(aroyl) pyridines such as Friedel–Crafts acylation using picolinoyl chloride,[17] constructing the pyridine from 1-aryl-1,2-propanedione,[18] the regiospecific electrophillic migration reaction of *N*-[1-(acyloxy)alkyl]pyridinium salts using sodium bis(trimethylsilyl)amide,[19] *ipso* acylation reactions using trimethylstannyl pyridines,[20] and the reaction of cyanopyridine with arylmagnesium halide or pyridyllithium with aryl cyanide.[21] Most of these methods suffer from disadvantages such as isomer/impurity formation, poor yields, long reaction times, cryogenic conditions, or the use of hazardous alkyllithium reagents.

Our efforts to develop an efficient process for these antihistamines resulted in new methods for making 2-(*N*-disubstituted amino) ethyltriphenylphosphonium bromides[22] and 2-(aroyl) pyridines. Herein we report a simple method for the preparation of 2-(aroyl) pyridines (**5a–l**) in high yields and purity by reacting *N*,*N*-dialkyl aryl amides (**4a–l**) with pyridylmagnesium chlorides (**3a–c**) at room temperature (Scheme 1 and Table 1). Song et al.[23] have reported that 2-pyridylmagnesium chloride (**3a**), prepared by reacting bromo/iodopyridine with isopropylmagnesium chloride in tetrahydrofuran (THF), was much more reactive than its lithium analog, and hence we chose this intermediate for making 2-(aroyl) pyridines. When we reacted **2**-pyridylmagnesium chlorides[24] with various carboxylic acid derivatives such as acid chlorides, carbonitriles, Weinreb amides, and *N,N*-dialkyl aryl amides under different reaction conditions to get 2-(aroyl) pyridines, we found that *N*,*N*-dialkyl arylamides react smoothly at room temperature to offer products without tertiary alcohol formation.



1 **2** **3** **4** **5**

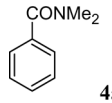
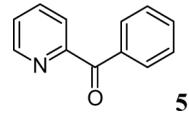
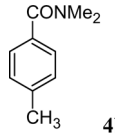
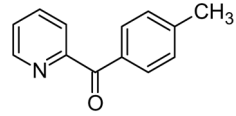
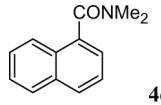
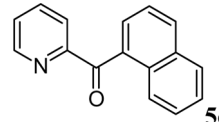
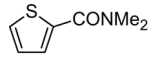
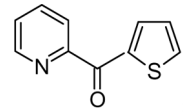
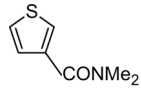
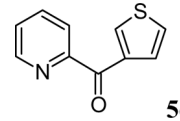
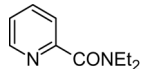
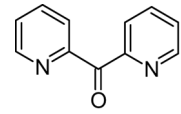
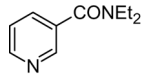
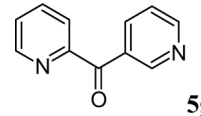
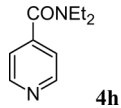
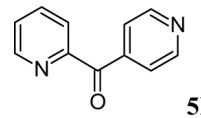
1a X = Br ; R = H

1b X = Br ; R = Me at C_6

1c X = I ; R = Br at C_5

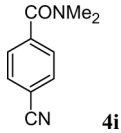
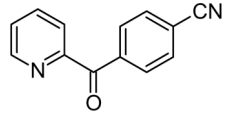
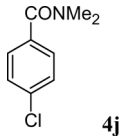
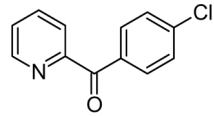
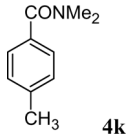
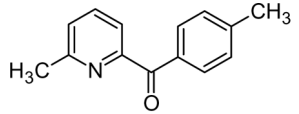
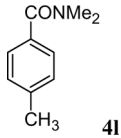
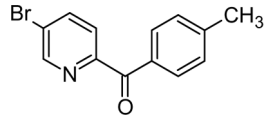
Scheme 1. Preparation of 2-(aroyl) pyridines.

Table 1. Yields of 2-(aryol) pyridines

Entry	Pyridyl-magnesium chloride	Disubstituted amide	2-(Aroyl) pyridine	Yield (%)
1	**3a**	 **4a**	 **5a**	88
2	**3a**	 **4b**	 **5b**	89
3	**3a**	 **4c**	 **5c**	92
4	**3a**	 **4d**	 **5d**	68
5	**3a**	 **4e**	 **5e**	73
6	**3a**	 **4f**	 **5f**	60
7	**3a**	 **4g**	 **5g**	87
8	**3a**	 **4h**	 **5h**	91

(*Continued*)

Table 1. Continued

Entry	Pyridyl-magnesium chloride	Disubstituted amide	2-(Aroyl) pyridine	Yield (%)
9	**3a**	 **4i**	 **5i**	80
10	**3a**	 **4j**	 **5j**	80
11	**3b**	 **4k**	 **5k**	89
12	**3c**	 **4l**	 **5l**	90

Unlike other alkyl and aryl magnesium halides as reported by Olah et al.,[9] pyridylmagnesium chlorides offer pure 2-(aroyl) pyridines without any tertiary alcohols even though amides have been added to Grignard reagent at room temperature. It appears that the intermediate (Grignard adduct) formed during the reaction is stable enough not to further react with one more molecule of pyridylmagnesium chloride, thereby avoiding the formation of tertiary alcohol. Although *N*,*N*-diethyl arylamides did not offer any advantage over *N*,*N*-dimethyl arylamides in terms of reactivity and yields, compounds **4f**, **4 h**, and **4g** have been prepared under anhydrous conditions using diethylamine because these amides are water soluble.

Using this methodology, we have prepared 2-aroyl pyridines containing naphthyl, thienyl, pyridyl, and substituted aryls, and the experimental data reveal that the electron-donating or electron-withdrawing group on

the arylamide moiety has no bearing on final ketone yields. We have also observed that arylamides react in preference to their carbonitrile counterparts, and this has been demonstrated by reacting **3a** with 4-cyano-*N*,*N*-dimethylbenzamide (**4i**) to afford pure 2-(4-cyanobenzoyl)pyridine (**5i**). While making **5i**, compound **3a** has been added to the amide **4i** to avoid any impurity formation. Further, all the raw materials employed are readily available and eliminate the usage of hazardous alkyl lithium and cryogenic conditions. Compound **5b**, which is an intermediate for triprolidine, has been prepared in multigram quantities with consistent yield and purity. Thus, this method is commercially viable and less cumbersome for preparation of 2-aroyl pyridines.

In conclusion, we have demonstrated an efficient approach for the preparation of a variety of 2-(aroyl) pyridines including the ones with cyano group on aryl ring. This method offers products with good purity in high yields and avoids the usage of lithium reagents and cryogenic conditions. We believe that this protocol will be useful in synthesizing various 2-(aroyl) pyridines as building blocks in organic synthesis.

EXPERIMENTAL

Melting points were determined on an Acro melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Thermo Nicolet Fourier transform (FT)-IR instrument in KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 200-MHz instrument. All chemical shift values are reported in δ units downfield from tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were recorded on a Q-TOF micro^{TM} instrument with AMPS MA $\times$ 10/6A system.

Experimental Procedure for 2-(Aroyl) Pyridines (5a–l)

To a stirred solution of isopropylmagnesium bromide (20% solution in THF, 1.1 equiv), bromopyridine **1a–c** (1.0 equiv) in tetrahydrofuran (THF) was added dropwise at 20–25°C under a nitrogen atmosphere. Stirring was continued at room temperature for 1 h and then substituted aryl amide **4a–l** (1.1 equiv.) was added dropwise over a period of 1 h. The reaction mixture was then quenched with ice-cold ammonium chloride solution and extracted with toluene. The toluene layer was dried over anhydrous Na_2SO_4 and evaporated to give the product.

Data

2-(Benzoyl) Pyridine (**5a**)

Compound **5a** (5.1 g, 88%) was obtained from **1a** (5 g, 31.6 mmol) and **4a** (5.1 g, 34.2 mmol). IR (KBr) υ_{max} 3058, 3004, 2923, 1666, 1577, 1446, 1404, 1311, 1280, 1245, 1161, 1091, 1045, 995, 937 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.52$ (m, 4H), 7.86 (dt, 1H, $J = 1.6$ Hz and 7.6 Hz), 8.02 (d, 2H, $J = 8.0$ Hz), 8.07 (d, 1H, $J = 7.6$ Hz), 8.70 (d, 1H, 2.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 125.1$, 126.6, 128.6, 131.4, 133.3, 136.7, 137.5, 148.9, 155.5, 194.3; HRMS (ES+) m/z calcd. for $C_{12}H_9NO$ $[M + H]^+$ 184.0762, obs. 184.0767.

2-(4-Toluoyl) Pyridine (**5b**)

Compound **1a** in 100 mL of THF (50 g, 316 mmol) was added dropwise at 20–25°C to a stirred solution of isopropylmagnesium bromide (20% solution in THF (174 mL, 34.8 mmol) under a nitrogen atmosphere. After stirring the reaction mixture at 20–25°C for 1 h, **4b** (56 g, 343 mmol) was added dropwise at the same temperature over a period of 1 h. The reaction mixture was then quenched in ice-cold ammonium chloride solution and stirred at room temperature for 30 min. The mixture was extracted with toluene (3×100 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to give **5b** (56 g, 89%). IR (KBr) υ_{max} 3055, 2920, 2866, 1662, 1604, 1577, 1434, 1407, 1307, 1284, 1242, 1157, 1091, 1041, 995, 933 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.43$ (s, 3H), 7.28 (d, 2H, $J = 8.4$ Hz), 7.47 (ddd, 1H, $J = 1.2$ Hz, 4.8 Hz, 7.6 Hz), 7.79–8.03 (m, 4H), 8.72 (d, 1H, $J = 4.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 22.1$, 124.9, 126.4, 129.3, 131.5, 134.1, 137.4, 144.2, 148.9, 155.8, 193.9; HRMS (ES+) m/z calcd. for $C_{13}H_{11}NO$ $[M + H]^+$ 198.0919, obs. 198.0929.

2-(1-Naphthoyl) Pyridine (**5c**)

Compound **5c** (6.8 g, 92%) was obtained from **1a** (5 g, 31.6 mmol) and **4c** (6.9 g, 34.6 mmol); mp 82–84°C. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.48$ (m, 4H), 7.71 (d, 1H, $J = 7.0$ Hz), 7.91 (m, 2H), 8.02 (d, 1H, $J = 8.0$ Hz), 8.16 (d, 1H, $J = 8.0$ Hz), 8.25 (m, 1H), 8.68 (d, 1H, $J = 4.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 124.1$, 124.5, 125.6, 126.2, 126.5, 127.4, 128.4, 129.9, 131.2, 132.1, 133.7, 134.6, 136.9, 149.1, 155.4, 196.5; HRMS (ES+) m/z calcd. for $C_{16}H_{11}NO$ $[M + Na]^+$ 256.0738, obs. 256.0739.

2-(2-Thienoyl) Pyridine (**5d**)

Compound **5d** (4.1 g, 68%) was obtained from **1a** (5 g, 31.6 mmol) and compound **4d** (5.3 g, 34.2 mmol). IR (KBr) υ_{max} 3058, 3008, 2923, 2858, 1643, 1581, 1504, 1465, 1434, 1407, 1357, 1307, 1284, 1245, 1149, 1084, 1045, 999, 918 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.17$ (dd, 1H, $J = 4.0$ Hz, 4.0 Hz), 7.45 (ddd, 1H, $J = 1.6$ Hz, 4.8 Hz, 7.8 Hz), 7.74 (dd, 1H, $J = 1.0$ Hz, 4.0 Hz), 7.86 (dt, 1H, $J = 1.6$ Hz, 7.8 Hz), 8.16 (d, 1H, $J = 7.8$ Hz), 8.39 (dd, 1H, $J = 1.0$ Hz, 4.0 Hz), 8.73 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 123.7$, 126.6, 127.5, 136.3, 136.6, 137.0, 139.8, 148.2, 153.8, 183.4; HRMS (ES+) m/z calcd. for $C_{10}H_7NOS$ $[M + H]^+$ 190.0326, obs. 190.0315.

2-(3-Thienoyl) Pyridine (**5e**)

Compound **5e** (4.4 g, 73%) was obtained from **1a** (5 g, 31.6 mmol) and **4e** (5.3 g, 34.2 mmol). IR (KBr) υ_{max} 3124, 3055, 3004, 2923, 2853, 1647, 1577, 1508, 1465, 1434, 1384, 1284, 1245, 1137, 1080, 1045, 995, 968 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.33$ (m, 1H), 7.47 (m, 1H), 7.83–7.92 (m, 2H), 8.12 (d, 1H, $J = 8.0$ Hz), 8.73 (d, 1H, $J = 4.4$ Hz), 8.84 (dd, 1H, $J = 1.0$ Hz, 2.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 124.7$, 125.6, 126.8, 129.8, 137.5, 140.2, 148.9, 155.6, 186.2; HRMS (ES+) m/z calcd. for $C_{10}H_7NOS$ $[M + H]^+$ 190.0326, obs. 190.0323.

2,2′-Dipyridyl Ketone (**5f**)

Compound **5f** (3.5 g, 60%) was obtained from **1a** (5.0 g, 31.6 mmol) and **4f** (6.1 g, 34.2 mmol). IR (KBr) υ_{max} 3355, 3055, 3004, 2927, 1685, 1581, 1465, 1434, 1319, 1280, 1242, 1180, 1149, 1095, 1045, 995, 945 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.45$ (ddd, 2H, $J = 1.0$ Hz, 4.6 Hz, 7.8 Hz), 7.90 (dt, 2H, $J = 1.6$ Hz, 7.8 Hz), 8.10 (d, 2H, $J = 7.8$ Hz), 8.76 (d, 2H, $J = 4.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 125.7$, 126.8, 137.2, 149.5, 154.6, 193.4; HRMS (ES+) m/z calcd. for $C_{11}H_8N_2O$ $[M + H]^+$ 185.0715, obs. 185.0710.

2,3′-Dipyridyl Ketone (**5g**)

Compound **5 g** (5.1 g, 87%) was obtained from **1a** (5 g, 31.6 mmol) and **4 g** (6.1 g, 34.2 mmol); mp 67–69°C. IR (KBr) υ_{max} 3066, 3031, 3008, 2981, 2931, 2873, 1666, 1581, 1469, 1431, 1415, 1334, 1311, 1288, 1249, 1199,

1168, 1141, 1122, 1087, 1029, 991, 941 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.45$ (dd, 1H, $J = 4.8$ Hz, 7.8 Hz) 7.54 (ddd, 1H, $J = 1.0$ Hz, 4.8 Hz, 7.8 Hz), 7.95 (dt, 1H, $J = 1.6$ Hz, 7.8 Hz), 8.16 (d, 1H $J = 7.8$ Hz), 8.43 (dt, 1H, $J = 1.6$ Hz, 7.8 Hz), 8.74 (d, 1H, $J = 4.8$ Hz), 8.80 (dd, 1H, $J = 1.6$ Hz, 4.8 Hz) and 9.39 (d, 1H, $J = 1.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 123.5$, 125.0, 127.3, 132.4, 137.7, 138.7, 149.1, 152.6, 153.3, 154.3, 192.6; HRMS (ES+) m/z calcd. for $C_{11}H_8N_2O$ $[M + H]^+$ 185.0715, obs. 185.0718.

2,4′-Dipyridyl Ketone (**5h**)

Compound **5 h** (5.3 g, 91%) was obtained from **1a** (5 g, 31.6 mmol) and **4 h** (6.1 g, 34.2 mmol); mp 123–126°C. IR (KBr) υ_{max} 3055, 3001, 2923, 1674, 1577, 1546, 1434, 1411, 1311, 1288, 1253, 1215, 1168, 1149, 1087, 1041, 991, 948 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.57$ (ddd, 1H, $J = 1.0$ Hz, 4.8 Hz, 7.8 Hz), 7.88–7.99 (m, 3H), 8.16 (d, 1H, $J = 7.8$ Hz), 8.74 (d, 1H, $J = 4.8$ Hz), 8.82 (dd, 2H, $J = 1.6$ Hz, 4.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 124.3$, 125.1, 127.5, 137.8, 143.3, 149.2, 150.6, 153.8, 192.5; HRMS (ES+) m/z calcd. for $C_{11}H_8N_2O$ $[M + H]^+$ 185.0715, obs. 185.0712.

2-(4-Cyanobenzoyl) Pyridine (**5i**)

Compound **5i** (5.2 g, 80%) was obtained from **1a** (5 g, 31.6 mmol) and **4i** (6.0 g, 34.4 mmol); mp 118–121°C. IR (KBr) υ_{max} 3058, 2923, 2854, 2233, 1670, 1581, 1558, 1465, 1434, 1404, 1311, 1284, 1242, 1195, 1153, 1091, 1045, 991, 968 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.55$ (ddd, 1H, $J = 1.0$ Hz, 4.8 Hz, 7.6 Hz), 7.79 (d, 2H, $J = 8.4$ Hz), 7.95 (dt, 1H, $J = 1.6$ Hz, 7.6 Hz), 8.15 (d, 1H, $J = 7.6$ Hz), 8.19 (d, 2H, $J = 8.4$ Hz), 8.72 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 116.2$, 118.6, 125.2, 127.4, 131.7, 132.2, 137.8, 140.3, 149.1, 154.1, 192.6; HRMS (ES+) m/z calcd. for $C_{13}H_8N_2O$ $[M + H]^+$ 209.0715, obs. 209.0706.

2-(4-Chlorobenzoyl) Pyridine (**5j**)

Compound **5j** (5.5 g, 80%) was obtained from **1a** (5 g, 31.6 mmol) and **4j** (6.3 g, 34.3 mmol); mp 66–69°C. IR (KBr) υ_{max} 3058, 1658, 1581, 1485, 1431, 1400, 1369, 1311, 1288, 1238, 1157, 1087, 1049, 1014, 995, 964 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.44$–7.54 (m, 3H), 7.92 (dt, 1H, $J = 1.6$ Hz, 8.0 Hz), 8.07 (d, 1H, $J = 7.8$ Hz), 8.08 (d, 2H, $J = 8.4$ Hz),

8.72 (d, 1H, $J = 4.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 125.1$, 126.8, 128.8, 132.9, 134.9, 137.6, 139.8, 148.9, 155.1, 192.8; HRMS (ES+) m/z calcd. for $C_{12}H_8ClNO$ $[M + Na]^+$ 240.0192, obs. 240.0186.

2-(p-Toluoyl)-6-Methylpyridine (**5k**)

Compound **5k** (5.5 g, 89%) was obtained from **1b** (5 g, 29.0 mmol) and **4b** (5.2 g, 31.9 mmol); mp 62–64°C. IR (KBr) υ_{max} 2920, 1654, 1600, 1585, 1458, 1407, 1373, 1319, 1238, 1164, 1118, 1095, 1033, 987, 948 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 2.43$ (s, 3H), 2.63 (s, 3H), 7.25–7.36 (m, 3H), 7.75 (d, 2H, $J = 4.4$ Hz), 8.01 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 21.6$, 24.4, 121.5, 125.5, 128.7, 131.2, 133.5, 136.9, 143.6, 154.9, 157.5, 193.5; HRMS (ES+) m/z calcd. for $C_{14}H_{13}NO$ $[M + Na]^+$ 234.0895, obs. 234.0899.

2-(p-Toluoyl)-5-bromopyridine (**5l**)

Obtained **5l** (4.3 g, 90%) from **1c** (5 g, 17.6 mmol) and **4b** (3.1 g, 19.0 mmol); mp 84–87°C. IR (KBr) υ_{max} 3047, 2916, 2858, 1658, 1604, 1558, 1454, 1407, 1361, 1299, 1280, 1230, 1184, 1157, 1122, 1087, 1006, 933 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 2.43$ (s, 3H), 7.29 (d, 2H, $J = 8.0$ Hz), 7.90–8.06 (m, 4H), 8.76 (d, 1H, $J = 2.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 22.2$, 124.5, 126.3, 129.4, 131.5, 133.7, 140.2, 144.5, 150.0, 154.0, 192.8; MS (EI) m/z 275 (M^+), 119 (100%).

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REFERENCES

1. (a) Brogden, R. N.; McTavish, D. Acrivastube: A review of its pharmacological properties and therapeutic efficacy in allergic rhinitis, urticaria and related disorders. *Drugs* **1991**, *41*, 927–940; (b) Findlay, J. W. A.; Coker, G. G. Aromatic compounds. European Patent 85959, 1983. *Chem. Abstr.* **1984**, *100*, 6345.
2. (a) Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M. Pyridyl-substituted alkamine ethers as antihistaminic agents. *J. Am. Chem. Soc.* **1949**, *71*, 887–890; (b) Sperber, N.; Papa, D.; Schwenk, E. Dialkyl aminoalkyl ethers of pyridine substituted carbinols. US Patent 266289, 1953. *Chem. Abstr.* **1955**, *49*, 8547; (c) Swain, A. P. Mono-(α-aryl)-substituted pyridine methanols. US Patent 2800485, 1957. *Chem. Abstr.* **1958**, *52*, 11419; (d) Nakajima, S.; Tanaka, I.;

Aka, T. 2-[4-Chloro-α-(2-dimethylaminoethoxy benzyl)]pyridine. JP 33005636, 1958. *Chem. Abstr.* **1959**, *53*, 105590.

3. (a) Cusic, J. W. Pyridylcarbinol ethers process of preparing same. US Patent 2606193, 1952. *Chem. Abstr.* **1953**, *47*, 44729; (b) Cusic, J. W. Phenyl pyridylcarbinol ethers. US Patent 2606194, 1952. *Chem. Abstr.* **1953**, *47*, 44730; (c) Tilford, C. H.; Shelton, R. S.; Van Campen, M. G. Histamine antagonists, basically substituted pyridine derivatives. *J. Am. Chem. Soc.* **1948**, *70*, 4001–4009; (d) Strauss, D. Dextrorotary (+) and levorotory (−) enantiomers of β-dimethylaminoethyl (phenylmethyl-2-pyridyl) carbinol ethers. DE 2906239, 1980. *Chem. Abstr.* **1981**, *94*, 47149.
4. McCarty, F. J.; Tilford, C. H.; Van Canpen, M. G.; William, S. Central stimulants, α,α-disubstituted 2-piperidinemethanols and 1,1-disubstituted hexahydrooxazolo-[3,4-a]pyridines. *J. Am. Chem. Soc.* **1957**, *79*, 472–480; (b) Kano, H.; Ogata, S. Diphenylhydroxymethyl substituted amines. JP 44031338, 1969. *Chem. Abstr.* **1970**, *72*, 100530.
5. (a) Fleming, R. W. (±)-Cis-α-[3-(2,6-dimethyl-1-piperidinyl)propyl]α-phenyl-2-pyridinemethanol. DE 2806654, 1978. *Chem. Abstr.* **1978**, *89*, 197346; (b) Fleming, R. W. α-Phenyl-2-pyridinemethanol compounds and method for their production. GB 1581096, 1980. *Chem. Abstr.* **1981**, *95*, 24821; (c) Hoefle, M. L.; Blouin, L. T.; Fleming, R. W.; Hastings, S.; Hinkley, J. M.; Mertz, T. E.; Steffe, T. J.; Stratton, C. S. Synthesis of antiarrhythmic activity of cis-2,6-dimethyl-α,α-diaryl-1-piperidinebutanols. *J. Med. Chem.* **1991**, *34*, 12–19.
6. (a) Kaiser, G.; Ross, S. T. Bronchodilating hydroxyphenyl-2-piperidinyl carbinols. DE 2047937, 1971. *Chem. Abstr.* **1971**, *75*, 35755; (b) Sankey, G. H.; Whiting, K. D. Cyclic adrenaline derivatives aryl-2-piperidyl carbinols. *J. Heterocycl. Chem.* **1972**, *9*, 1049–1055; (c) Asem, A. J.; Hansen, L. K. The absolute configuration of rimiterol, a sympathomimetic bronchodilator: The crystal structure of (R,R)-ethoxy (3,4-dihydroxyphenyl) (2-piperidinyl) methane hydrochloride. *Acta Chem. Scand., Series B* **1988**, *42*, 216–222.
7. (a) Benezra, S. A.; Yang, C.-H. Triprolidine hydrochloride. *Anal. Profiles Drug Substances* **1979**, *8*, 509–528; (b) Benezra, S. A.; Yang, C.-H. Triprolidine hydrochloride. *Anal. Profiles Drug Substances* **1979**, *8*, 509–528; (b) Adamson, D. W. Heterocyclic allylamines. US Patent 2,712,020, 1955. *Chem. Abstr.* **1955**, *49*, 4026; (c) Adamson, D. W. Alkyl substituted antihistamines. US Patent 2,712,023, 1955. *Chem. Abstr.* **1955**, *49*, 10377; (d) Adamson, D. W.; Barrett, P. A.; Billing, J. W.; Jones, T. S. G. Aminoalkyl tertiary carbinols and derived products: Stereochemistry of some 1-phenyl-1-(2-pyridyl) prop-1-enes and some 3-(tertiaryamino)-phenyl-1-(2-pyridyl)-1-propenes carrying additional substituents. *J. Chem. Soc.* **1958**, 312–324; (e) Adamson, D. W. Trans-1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidino-1-propene. DE 1227464, 1966. *Chem. Abstr.* **1967**, *66*, 37780.
8. (a) Rydh, T. O. V.; Uttf, C. B. J. N,N-dimethyl-3-(4-bromophenyl)-3-(-pyridyl) allylamine dihydrochloride monohydrate. BE 842368, 1976. *Chem. Abstr.* **1977**, *87*, 102173; (b) Baeckvall, J. E.; Nordberg, R. E.; Nystroem, J. E.; Hoegberg, T.; Ulff, B. Synthesis of 3-aryl-3-pyridylallylamines related to zimeldine via

palladium catalysed amination. *J. Org. Chem.* **1981**, *46*, 3479–3483; (c) Hoegberg, T.; Ulff, B.; Renyi, A. L.; Ross, S. B. Synthesis of pyridyl allylamines related to zimeldine and their inhibition of nevronal monoamine uptake. *J. Med. Chem.* **1981**, *24*, 1499–1507; (d) Hoegberg, T.; Ulff, C. B. J. A novel process for preparing bromophenyl pyridyl allylamines. European Patent 52588, 1982. *Chem. Abstr.* **1982**, *97*, 127511.

9. Olah, G. A.; Surya Prakash, G. K.; Massoud, A. Improved preparation of aldehydes and ketones from N,N-dimethyl amides and Grignard reagents. *Synthesis* **1984**, 228–230.
10. Steven, N.; Weinreb, S. M. N-methoxy, N-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981**, *21*, 3815–3818.
11. Itsuno, S.; Miyazaki, K.; Ito, K. Reactions of aldehydes O-alkyloximes with organometallic compounds. *Tetrahedron Lett.* **1986**, *27*, 3033–3036.
12. Strekowski, L.; Wydra, R. L.; Cegla, T. M.; Czarny, A.; Patterson, S. Efficient preparation of ketones from N-(ethoxymethylene) aniline and organometallic reagents. *J. Org. Chem.* **1989**, *54*, 6120–6123.
13. Trecourt, T.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quenguiner, G. Cross coupling between pyridylmagnesium chloride and hetero aromatic halides. *Tetrahedron* **2000**, *56*, 1349–1360.
14. Weiberth, F. J.; Hall, S. S. Copper(I) activated addition of Grignard reagents to nitriles: Synthesis of ketimines, ketones, and amines. *J. Org. Chem.* **1987**, *52*, 3901–3904.
15. Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. An efficient synthesis of diaryl ketones by iron catalysed arylation of aroyl cyanides. *Angew. Chem. Int. Ed.* **2004**, *43*, 2968–2970.
16. Comis, D. L.; Mantlo, N. B. Synthesis of 3-acylpyridines utilizing a Friedel–Crafts reaction. *Tetrahedron Lett.* **1983**, *24*, 3683–3686.
17. Ivone, C.; Joseph, M. Synthesis of 1-methyl-2-hydroxyiminomethylaryl pyridinium salts with potential as acetyl cholinesterase reactivators. *Heterocycl. Commun.* **1995**, *1*, 403–410.
18. De Kimpe, N.; Keppens, M.; Fonck, G. A new efficient synthesis of pyridines. *Chem. Commun.* **1996**, *5*, 635–636.
19. Anders, E.; Boldt, H. G.; Clark, T.; Funchs, R.; Gassner, T. N-[(1-Acetyloxy)-alkyl] heteroaromatic ring systems. *Chem. Ber.* **1986**, *119*, 279–296.
20. (a) Yamamoto, Y.; Yanagi, A. A simple method for introduction of only groups into pyridine nuclei via trimethylstannyl pyridines and quinolines. *Heterocycles* **1982**, *19*, 41–44; (b) Yamamoto, Y.; Yanagi, A. Studies on organometallic compounds reaction of trimethylstannyl azines with acyl chlorides: A novel carbon–carbon bond formation in pyridine nuclei. *Chem. Pharm. Bull.* **1982**, *30*, 2003–2010; (c) Yamamoto, Y.; Tanaka, T.; Ouchi, H.; Miyakama, M.; Morita, Y. Carbon functionalizations on pyridine ring via trimethylstannyl derivatives: An example of fusaric acid synthesis. *Heterocycles* **1995**, *41*, 817–825; (d) Yamamoto, Y.; Ouchi, H.; Tanaka, T. Studies on organometallic compounds: Simple and mild method for preparation of α-pyridine carboxylates and α-pyridyl ketones via trimethyl stannyl derivatives. *Chem. Pharm. Bull.* **1995**, *43*, 1028–1030.

21. Coker, G. G.; Findlay, W. A. 1,1-Diaryl propenyl-3-(1-pyrrolidino-2-carboxylic acids, derivatives thereof, and their anti-histaminic properties. US Patent 4610995, 1986; *Chem. Abstr.* **1986**, *104*, 50792.
22. Rao, G. V.; Reddy, G. C. Preparation of 2-(N-disubstituted amino) ethyl triphenylphosphonium bromides. *Tetrahedron Lett.* **2008**, *49*, 824–826.
23. Song, J. J.; Yee, N. K.; Tan, Z.; Xu, J.; Kapadia, S. R.; Senanayake, C. H. Synthesis of 5-bromopyridyl-2-magnesium chloride and its application in the synthesis of functionalized pyridines. *Org. Lett.* **2004**, *6*, 4905–4907.
24. Mongin, F.; Trecourt, F.; Quenguiner, G. Directed lithiation of unprotected pyridine carboxylic acids. *Tetrahedron Lett.* **1999**, *40*, 5483–5486.