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The Preparation of Substituted Hydroxyphenyl-pyridyl-ethanols and α-Hydroxyphenyl-α-methylpyridineethanols by the Condensation of 2-, 3-, or 4-Picolyllithium with Select Hydroxy-benzaldehydes and 4-Hydroxyacetophenone

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THE PREPARATION OF SUBSTITUTED HYDROXYPHENYL-PYRIDYL-ETHANOLS AND α-HYDROXYPHENYL-α-METHYLPYRIDINEETHANOLS BY THE CONDENSATION OF 2-, 3-, OR 4-PICOLYLLITHIUM WITH SELECT HYDROXY-BENZALDEHYDES AND 4-HYDROXYACETOPHENONE

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ABSTRACT: 2-, 3-, or 4-Picolyllithium was prepared in excess lithium diisopropylamide and condensed with several hydroxy-benzaldehydes and 4-hydroxyacetophenone to afford substituted hydroxyphenyl-pyridyl-ethanols and α-hydroxyphenyl-α-methylpyridineethanols. In two instances, 3-picolyllithium condensed with aldehydes to presumably form the hydroxyphenyl-pyridyl-ethanol, which underwent linear dehydration to the substituted pyridyl-ethylenyl-phenol.

Picolines have been monometalated with lithium diisopropylamide (LDA) and other bases[1-3], and the resulting picolyllithium or related carbanion-type intermediates have undergone aldol-type condensations with a variety of ketones and aldehydes to afford substituted pyridineethanol products. Specifically, a recent report[1] described the metalation of 3- and 4-picoline with LDA at -50°, which was followed by condensation with 4-methoxybenzaldehyde, starting at -20°. The resulting methoxyphenyl-pyridyl-ethanols were then treated with boron trifluoride/dimethyl sulfide complex in order to cleave the methoxy group and free the phenol, resulting in the hydroxyphenyl-pyridyl-ethanol. In an earlier report[2a], 3-picoline

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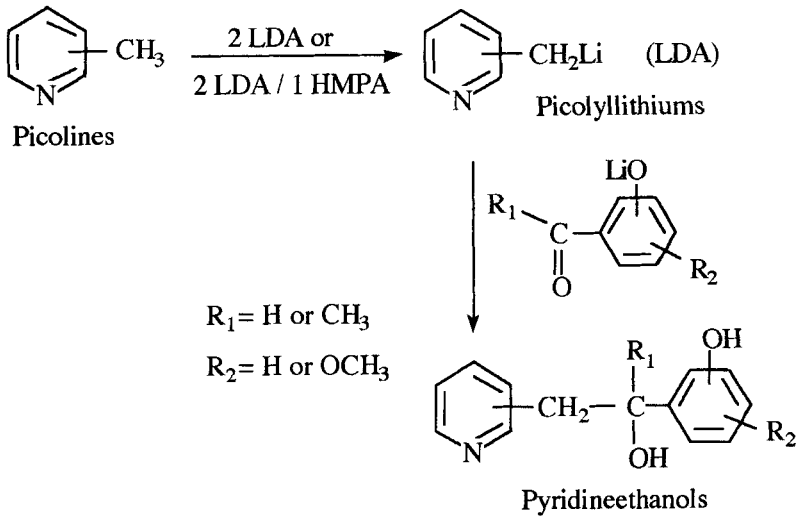
was metalated with LDA in the presence of hexamethylphosphoramide (HMPA) at 0° to afford a 3-picolyllithium intermediate that was condensed with a variety of ketones, such as benzophenone, and a single aldehyde, benzaldehyde. Two additional reports[4] dealt with the preparation of select hydroxyphenyl-pyridyl-ethanols involving condensation of pyridineacetic acids with substituted benzaldehydes.

In related studies[5,6], sodium or lithium ethyl benzoylacetate, or lithium methyl salicylates and lithium methyl 4-hydroxybenzoate underwent Claisen-type condensations with several polylithiated intermediates [*e.g.*, C(α),N-dilithio-carbalkoxyhydrazones]. The carboethoxy group of the benzoylacetate enolate, and the carbomethoxy group *ortho* or *para* to the phenoxide anion were in a resonance position thus diminishing the electrophilicity of the carboxy carbon. The condensation of this ester group with the carbanion-type nucleophile was initially expected to be more difficult than other condensations of this type. Recently[7], we have been able to report the condensation of dilithium α-phenyl-*ortho*-toluate and dilithium *ortho*-toluate with aldehydes and ketones, such as 3,4-dichlorobenz-aldehyde and 2-hydroxyacetophenone, which was followed by cyclodehydration to the desired dihydroisocoumarins. The phenoxide anion of 2-hydroxyacetophenone was in a resonance position to diminish the electrophilicity of the carbonyl carbon, and the reaction was also initially envisioned to be more challenging.

In this study, our attention has been directed to the monolithiation of 2-, 3-, and 4-picolines, and the possible aldol-type condensations of the picolyllithium intermediates with lithiated hydroxy-benzaldehydes and 4-hydroxyacetophenone in order to make substituted hydroxyphenyl-pyridyl-ethanols and α-hydroxyphenyl-α-methylpyridineethanols. We were interested in conveniently preparing enough products for biological testing and investigating their potential for further reactions in a multi-step synthesis (E1, photocyclization, etc.). In our earlier studies[8]

involving the condensation of multiple anion-type intermediates with aldehydes and ketones, we noted that the success of these aldol-type condensations depends upon many of the following parameters: [1] the type of entry compound used (*e.g.*, picoline, hydrazone, other); [2] the method of anion formation (*e.g.*, base, temperature, solvent, etc.); [3] the aldehyde or ketone employed for condensation; [4] the condensation time of the anion-type intermediate with a particular carbonyl compound; and [5] where appropriate, the rapidity of acid neutralization of the solution containing the condensation intermediate.



The picolines used during this investigation are readily available [9], and the 2- and 4-picolines were easily metalated with excess LDA (picoline:LDA: electrophile - 1:2:1),while the 3-picoline required the use of HMPA (picoline:LDA: HMPA:electrophile - 1:2:1:1). Each picolyllithium intermediate was condensed with lithiated hydroxy-benzaldehydes (*e.g.*, salicylaldehyde, 3- and 4-hydroxybenzaldehyde, etc.) to products **1-5**, **9**, and **10**; 2- and 4-picolyllithium were condensed with lithiated 4-hydroxyacetophenone to products **7** and **8**

(Table). A condensation time of 12 - 14 hours was necessary and was followed by rapid neutralization with 3M acetic acid. After the pH of the mixture was adjusted to approximately 7 by the addition of base, the products were isolated and usually purified by recrystallization from routine solvents (footnote, Table).

General Experimental Procedure:

In a typical experiment, a three-necked, round-bottomed flask, equipped with a stir bar, nitrogen inlet tube, and side-armed addition funnel (*e.g.*, 125 mL), was cooled in an ice-water bath and charged with 0.0525 mol of *n*-butyllithium, which was followed by addition of an equivalent amount of diisopropylamine (0.0525 mol) dissolved in 35-45 mL of dry tetrahydrofuran (THF - sodium, benzophenone). The treatment of the resulting LDA depended on the picoline used. When 3-picoline was metalated, the next reagent added to the LDA solution was HMPA (0.025 mol) dissolved in 25-35 mL of THF. The HMPA was omitted for 2- and 4-picolines. The solution of LDA, or LDA/HMPA, was stirred at 0° for 20 min., and then followed by the addition during 5 min. of the desired picoline (0.025 mol.) dissolved in 25-35 mL of THF. The usual metalation time was 30 min. at 0°. The ice bath was then removed, and the aldehyde or ketone, dissolved in 100-125 mL of THF, was slowly added to the well stirred solution during 30-45 minutes. Upon addition of the aldehyde or ketone electrophilic reagent, the stirred mixture usually thickened, because precipitation occurred. If extensive thickening was observed, the addition rate of the picoline solution was slowed to 60 - 75 minutes. Also, enough dry THF (up to 150-200 mL) was added to ensure continued stirring of the mixture overnight (*ca.*, 12 - 14 hr., N_2). The mixture/ solution was then poured into a large flask containing 100 mL of 3 M acetic acid and about 100 g of ice, which was followed by the addition of 100 mL of solvent grade ether. The pH was adjusted (pH paper) to 7 by the slow addition of potassium hydroxide solution (*ca.*, 10-20%), which was followed by the separation

TABLE - Substituted Hydroxyphenyl-Pyridyl-Ethanols and α-Hydroxyphenyl-α-Methylpyridineethanols

Compd. No.	Picoline Used[a]	Aldehyde/Ketone Used[a]	Mol. Formula[b] Product	%Yield/Mp°C[c]
1	3-	Salicylaldehyde	$C_{13}H_{13}NO_2$	45/167-69[d]
2	3-	4-Hydroxybenzaldehyde	$C_{13}H_{13}NO_2$	19/159-60[e]
3	4-	4-Hydroxybenzaldehyde	$C_{13}H_{13}NO_2$	92/171-73[f]
4	2-	4-Hydroxybenzaldehyde	$C_{13}H_{13}NO_2$	39/169-71[f]
5	4-	3-Hydroxybenzaldehyde	$C_{13}H_{13}NO_2$	20/182-83[d]
6	2-	3-Hydroxybenzaldehyde	$C_{13}H_{13}NO_2$	6/148-50[e]
7	2-	4-Hydroxyacetophenone	$C_{14}H_{15}NO_2$	89/150-53[e]
8	4-	4-Hydroxyacetophenone	$C_{14}H_{15}NO_2.H_2O$	56/151-53[e]
9	4-	Isovanillin	$C_{14}H_{15}NO_3$	26/147-49[e]
10	2-	Isovanillin	$C_{14}H_{15}NO_3$	10/180-83[f]
		Substituted Pyridyl-Ethylenyl-Phenols[a,b]		
11	3-	3-Hydroxybenzaldehyde	$C_{13}H_{11}NO.1/2\ H_2O$	3/147-49[h,i]
12	3-	5-Bromosalicylaldehyde	$C_{13}H_{10}BrNO$	37/235-36[f]

[a]See ref. 9. [b]See ref. 10. [c]Melting points were obtained in a Mel Temp apparatus in open capillary tubes and are uncorrected. [d]Recryst. from ethanol/benzene. [e]Recryst. from ethanol/water. [f]Recryst. from ethanol. [g]Recryst. from ethanol/water. [h]Column chromat., silica gel, 80:20, hexanes:ethyl acetate; HPLC, 60:40, methanol:water. [i]GC-MS, (M^+, 197), found: 197; see: ref. 13.

of the two phases. The aqueous phase was extracted with solvent grade ether and/or THF (2 X 100 mL), and the organic layers were combined and dried ($MgSO_4$). If a solid formed prior to the addition of the drying agent, the drying step was omitted. The solution was filtered from the drying agent, when applicable, and the solvents were removed by rotary evaporator, or evaporation in a ventilated hood. If an oil resulted, it was taken up in ethanol, and solids precipitated on standing (room temp. or refrigeration). They were filtered and recrystallized from ethanol, ethanol/water, or ethanol/benzene (Table).

The melting point of 1-(4-hydroxyphenyl)-2-(4-pyridyl)ethanol **3**[10,11], mp 171-173° agreed well with that reported for this compound [lit.[1] mp, 171-172.5°]; but the melting point of 1-(4-hydroxyphenyl)-2-(3-pyridyl)ethanol **2** [10,11], mp 159-160° differed from the literature report for this material [lit.[1] mp, 143-45°]. Abstract citations[4] reported melting points for hydroxyphenyl-pyridyl-ethanols **5**, mp 182-83° [lit.[4b,c]mp, 113-14°] and **6**, mp 148-50° [lit[4b,c]mp, 90-91°] that differed from ours, and based upon the wording of the abstract, they were most probably the melting points of the dehydration products, pyridyl-ethylenyl-phenols. Support for the structure of **1 - 10** and other products (**11** & **12**) were then obtained from ^1H nmr and infrared spectra, in addition to combustion analyses[10,11]. Hydroxy-phenyl-pyridyl-ethanols **2 - 6**, **9**, and **10** displayed discernible methylene doublets, with estimated chemical shifts ranging from δ 2.85 - 3.02 ppm (d, $-CH_2-$), with little or no additional splitting. Coupled triplet absorptions for methine hydrogens usually displayed additional splitting; but chemical shifts for compounds **2**, **6**, and **9** could easily be estimated ranging from δ 4.67 - 4.90 ppm (t, CH). α-Hydroxy-phenyl-α-methyl- pyridineethanols, **7** and **8**, displayed anticipated absorptions for methyl δ 1.43 - 1.48 (s, CH_3), and methylene δ 2.47 - 2.97 (s, CH_2) moieties. For all compounds reported, the aromatic absorptions were recorded as two distinguishable multiplets, δ 6.33 - 7.59 and 8.18 -8.57 ppm, with the further

downfield multiplet attributed to the hydrogens closest to the nitrogen of the pyridine ring. Infrared spectra of **1-10** [10] displayed broad OH absorptions, 3200 - 3500 cm^{-1}, with a conspicuous and sharp OH absorption observed at 3511 cm^{-1} in substituted pyridineethanol **8**, which is a monohydrated compound[11]. Additional satisfactory combustion analysis (for C, H, and/or N) were also obtained[11].

When 3-picoline was metalated with LDA/HMPA and condensed with 3-hydroxybenzaldehyde or 5-bromosalicylaldehyde, pyridyl-ethylenyl-phenols **11** (3%) and **12** (37%), respectively were isolated instead[10-12] of substituted pyridineethanols.

The yields of hydroxyphenyl-pyridyl-ethanols **1 - 6**, **9** and **10**, and α-hydroxy-phenyl-α-methylpyridineethanols **7** and **8** ranged from 6-92%, which indicates that the general experimental procedure is usually satisfactory for the expedient preparation of 0.5-1.0 gram quantities of the desired products (double quantities of reactants for **6**), that can be purified by recrystallization from routine solvents. This may not necessarily represent the optimum conditions for the preparation of an individual compound. Also, elimination of water to the substituted ethylene did not usually occur, and secondary or tertiary alcohols **1 - 10** were isolated. Substituted pyridyl-ethylenyl-phenol **11** could not be purified by recrystallization after work-up, and chromatographic separations (footnote, Table) in addition to extensive handling of this material may have facilitated elimination of water from its hydroxyphenyl-pyridyl-ethanol precursor. For **12**, we do not have a full explanation for dehydration of its hydroxyphenyl-pyridyl-ethanol precursor to the substituted pyridyl-ethylenyl-phenol. This material also resulted from the more challenging condensation of 3-picoline with 5-bromosalicylaldehyde, and its purification required additional heating time of crude product in recrystallization solvent, ethanol.

Several additional points are noted: (1) α-hydroxyphenyl-α-methyl-pyridineethanols **9** and **10** resulted from the condensation of 2- and 4-picolyl-lithium with 4-hydroxyacetophenone, which is another successful condensation of some of our lithiated intermediates[7] with this type of nucleophilic-electrophilic reagent[6-8]; (2) substituted pyridineethanols can be made in a single step[1] by the condensation of lithiated hydroxy-benzaldehydes or 4-hydroxyacetophenone, with monolithiated picolines, where the lithiated phenols (for the preparation of compounds **1 - 4, 7, 8** & **12**) from 2-hydroxy- and 4-hydroxybenzaldehydes, or 4-hydroxyacetophenone have diminished reactivity due to the resonance position of the phenoxide relative to the carbonyl carbon; and (3) the experimental procedure is straight forward so that someone not necessarily familiar with strong-base procedures can be successful with the reactions.

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9. 2-, 3-, and 4-Picoline, and aldehydes and ketones were obtained from Aldrich Chemical Co. The picolines were used immediately after receipt and opening.

10. Infrared spectra were obtained from a Mattson Polaris FT-Infrared Spectrometer. ^{1}H nmr for **1 - 10** and **12** were obtained from a Varian Associates, EM-360L Nuclear Magnetic Resonance Spectrometer, and chemical shifts are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. The ^{1}H nmr for compound **11** was obtained from a 400 MHz, Varian Associates VXR multi-probe nuclear magnetic resonance spectrometer. Compound No., ir; nmr: Compd. **1**; ir (paraffin oil) 3400 cm^{-1} broad and shoulder (OH); nmr (DMSO-d_6), δ 2.58 - 2.93 (m, CH_2), 4.88 - 5.27 (m, CH), 6.53 - 7.70 and 8.18 - 8.52 (m, ArH), and 9.47 (s, ArOH). Compd. **2**; ir (paraffin oil) 3503 cm^{-1} broad and shoulder; nmr (DMSO-d_6 and $CDCl_3$), 2.93 (d, CH_2), 4.75 (t. CH), 6.58 - 7.42 and 8.25 - 8.55 (m, ArH). Compd. **3**; ir (paraffin oil) 3380 cm^{-1} broad and shoulder (OH); nmr (DMSO-d_6), 2.88 (d, CH_2), 4.95 - 5.23 (m, CH), 6.50 - 7.23 and 8.20 - 8.50 (m, ArH), and 9.23 (s-broad, ArOH). Compd. **4**; ir (paraffin oil),

3200 cm^{-1}(shoulder of paraffin oil absorption); nmr (DMSO-d_6), 3.00 (d, CH_2), 4.67 - 5.13 (m, CH), 6.43 - 7.83 and 8.40 - 8.63 (m, ArH), and 9.27 (s, ArOH). Compd. **5**; ir (KBr), 3427 and 3557 cm^{-1}(OH and ArOH); nmr (DMSO-d_6 and $CDCl_3$), 2.90 (d, CH_2), 4.75 (t, CH), 6.58 - 7.37 and 8.37 - 8.57 (m, ArH). Compd. **6**; ir (KBr), 3418 cm^{-1}; nmr (DMSO-d_6), 3.02 (d, CH_2), 4.90 (t, CH), 6.33 - 7.93 and 8.30 - 8.67 (m, ArH), and 9.19 (s broad, ArOH). Compd. **7**; ir (paraffin oil), 3166 cm^{-1}(OH, with shoulder); nmr (DMSO-d_6 and $CDCl_3$), 1.43 (s, CH_3), 2.47 (s, CH_2), 3.17(s, OH), 6.60 - .95 and 8.40 -8.57 (m ArH). Compd. **8**; ir (paraffin oil), 3511 (sh,OH from H_2O), and 3332 and 3148 cm^{-1}(shoulders of paraffin oil absorption) ; nmr (DMSO-d_6 and $CDCl_3$), 1.48 (s, CH_3), 2.97 (s, CH_2), 6.62 - 7.33 and 8.20 - 8.45 (m, ArH). Compd. **9**; ir (KBr), 3460 cm^{-1}; nmr (DMSO-d_6), 2.85 (d, CH_2), 3.73 (s, OCH_3) 4.67 (t, CH), 6.57 - 7.33 and 8.27 - 8.58 (m, ArH), and 8.67 -9.05 (bm, ArOH). Compd. **10**; ir (paraffin oil), 3200-3300 cm^{-1}(OH, shoulder of paraffin oil absorption); nmr (DMSO-d_6), 2.99 (d, CH_2), 3.72 (s, OCH_3), 5.10 5.33 (m, CH), 6.68 - 7.77 and 8.42 - 8.58 (m, ArH), and 8.88 (s-broad, ArOH). Compd. **11**; nmr (DMSO-d_6), δ 7.06 (s, vinyl, J = 17), 7.14 (s, vinyl, J = 17), 7.89 (dd, J = 1.5 and 5, H-2 pyridyl ring), 8.50 (d, J = 0 and 1.8, H-6 pyridyl ring), 6.80-7.38 (other ArH), and 8.76 (s, ArOH). Compd. **12**; nmr (DMSO-d_6), 6.85, 7.00, 7.23 - 8.17 and 8.43 - 8.93 (vinyl and ArH), and 10.33 (s, ArOH).

11. Microanalyses for C, H, and N were obtained from Quantitative Technologies, Inc., Box 470, Salem Industrial Park, Whitehouse, NJ 07940 [Compd. No. from Table]. Calcd. for **1**: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.11; N, 6.38. Calcd. for **2**: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.27; H, 6.34; N, 6.17. Calcd. for **3**: N, 6.51. Found: N, 6.45. Calcd. for **4**: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.19; H, 6.04; N, 6.42. Calcd. for **5**: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.63; H, 6.08; N, 6.40. Calcd. for **6**: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.71; H, 6.20; N, 6.32. Calcd. for **7**: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.95; H, 6.59; N, 6.00. Calcd. for **8** ($C_{14}H_{15}NO_2.H_2O$): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.00; H, 6.81; N, 5.47. Calcd. for **9**: C, 68.28; H, 6.14; N, 5.69. Found: C, 68.43; H, 6.15; N, 5.61. Calcd. for **10**: C, 68.54; H, 6.15; N, 5.73. Found: C, 68.42; H, 6.25; N, 5.68. Calcd. for **11** ($C_{13}H_{11}NO.1/2\ H_2O$): C, 75.71; H, 5.86; N, 6.79. Found:

C, 76.93; H, 5.91; N, 6.67. Calcd. for **12** ($C_{13}H_{10}BrNO$): C, 56.55; H, 3.65; N, 5.07. Found: C, 56.46; H, 3.57; N, 4.85.

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