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# Synthesis of 3 or 4-Substituted Pyridine-2, 6-Dicarboxylic Acid

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**Abstract:** Various 4-alkoxypyridine-2, 6-dicarboxylic acids were synthesized starting from 2, 6-lutidine. Through aldol condensation and Michael addition, various 4-arylpyridine-2, 6-dicarboxylic acids were synthesized starting from aromatic aldehydes and 2-acetylfuran.

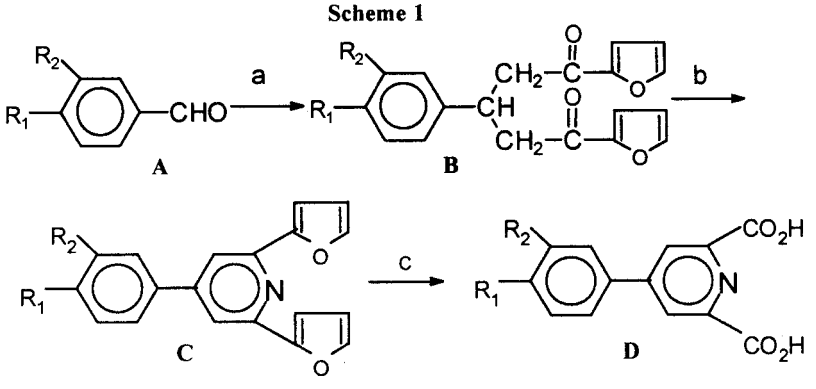
**Keywords:** Michael reaction, 2, 6-lutidine analogues, substituted pyridine-2, 6-dicarboxylic acids.

Time-resolved circularly polarized luminescence (CPL) studies have been particularly successful at measuring differences in quenching rate constants in certain diastereomeric donor-acceptor systems[1] It is anticipated that these types of experiments may be applied to more complex systems involving racemic lanthanide emitter complexes in a solution containing transition metal complexes enantioselectively bound to DNA[2].

However, the luminophores were only confined to Ln $(DPA)_3^{3-}$ and Ln $(CDA)_3^{3-}$ (Ln=$Eu^{3+}$, $Tb^{3+}$, DPA=dipicolinate dianion, CDA=chelidamate). Effects of ligand size, shape, configuration and electron in the luminophores have not been studied in detail. It has certainly limited applications of the technique. Therefore, we have designed and successfully synthesized a series of 3 or 4-substituted pyridine-2, 6-dicarboxylic acid derivatives.

We prepared 4-arylpyridine-1, 3-dicarboxylic acids *via* 3 steps from the aromatic aldehydes and 2-acetylfuran. The overall sequence of reactions is shown in **Scheme 1**.

**Scheme 1**



Reagents and conditions: (a) 2-acetylfuran, NaOH/$CH_3OH$, reflux, 4~7h. (b) i. $NH_2OH·HCl$, n-butanol, reflux, 8h. ii. silica gel, $CH_2Cl_2$/hexane(1:1). (c) $KMnO_4$, $C_6H_6/H_2O$, PEG600, reflux, 3h.

**Table 1** Reaction of aromatic aldehydes with 2-acetylfuran in basic solution

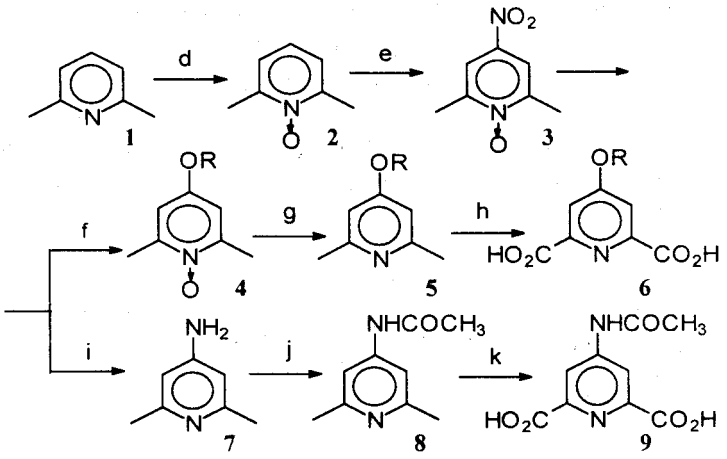
| Entry | Aromatic aldehyde | | Temp | Time | Yield(compound **B**) |
|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | (°C) | (h) | (%) |
| $A_1$ | H | H | reflux | 4 | 61($B_1$) |
| $A_2$ | -$OCH_3$ | H | reflux | 4 | 54($B_2$) |
| $A_3$ | H | -$NO_2$ | reflux | 4 | 66($B_3$) |
| $A_4$ | -$N(CH_3)_2$ | H | reflux | 4 or 7 | f |
| $A_5$ | β-Naphthaldehyde | | reflux | 4 or 7 | g |

[f]product $B_4$ was not obtained, product of aldol reaction also was not obtained.
[g]product $B_5$ was not obtained, only product of aldol reaction was gave.

The cyclization of compound B could be carried out using ammonium acetate in methanol in rather low yield. Oxidation of the furan rings could be carried out using ozone/hydrogen peroxide but dilute nitric acid was more convenient and gave higher yield. A furan ring has also been oxidized to carboxylic acid using potassium permanganate in acetone at room temperature for 5 days, or using potassium permanganate in t-butanol and water reflux for 17 h3.

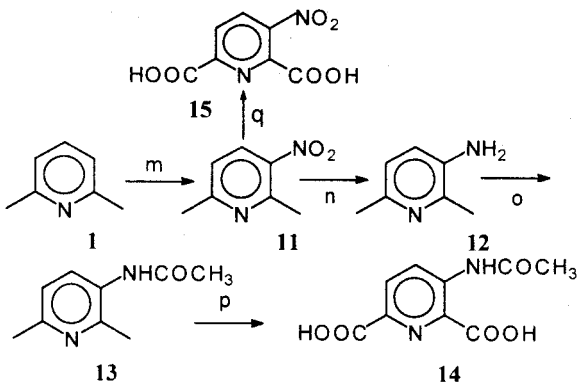
First, it involves an aldol condensation, followed by a Michel addition reaction to form a 1, 5-diketone. Then 1, 5-diketone condenses with hydroxylamine to form N-hydroxyl dihydropyridine, which is accompanied by simple elimination of H2O, giving pyridine C.

**Scheme 2**




Reagents and conditions: (d) 30%$H_2O_2$, $CH_3COOH$, 80°C, 12h. (e) conc. $H_2SO_4$, conc. $HNO_3$, 90°C, 7h.[4] (f) Na, absulate ROH $f_a$: [$CH_3OH$, $f_b$: $CH_3CH_2OH$, $f_c$: $CH_3CH_2CH_2OH$, $f_d$: $(CH_3)_2CHOH$, $f_e$: $CH_3(CH_2)_3OH$, *etc.*], reflux, 10~15h. (g) Fe, $CH_3COOH$, 100°C, 1~1.5h. (h) $KMnO_4$, $H_2O$, reflux, 17h. (i) $NaHSO_3$, $CH_3CH_2OH/H_2O$, reflux, 0.5h.[5] (j) $(CH_3CO)_2O$, $CH_3COOH$, reflux, 1h. (k) $KMnO_4$, $H_2O$, reflux, 17h.

**Scheme 3**




Reagents and conditions: (m) conc. $H_2SO_4$, $KNO_3$, 125°C, 18h. (n) Fe, $CH_3COOH$, 100°C, 1.5h. (o) $(CH_3CO)_2O$, $CH_3COOH$, reflux, 1h. (p) $KMnO_4$, $H_2O$, reflux, 17h. (q) $KMnO_4$, t-butanol, $H_2O$, reflux, 17h.

To prepare a series of 3 or 4-substituted pyridine-2, 6-dicarboxylic acid, we have designed two synthetic schemes, as shown in Scheme 2 and Scheme 3. Compared with 2, 6-lutidine, 2, 6-lutidine-N-oxide is easily nitrated to form 3-nitro-2, 6-lutidine, and the nitro-group in 3 position can not be replaced by anions. 2, 6-lutidine-N-oxide is readily nitrated only to give 4-nitro-2, 6-lutidine-N-oxide, and the nitro-group leave readily, it will make the 4 position vulnerable for nucleophilic substitution (Scheme 2).

The experimental results showed that the nitro-group in 4-nitro-2, 6-lutidine-N-oxide can be readily replaced by anions [CH3O-, CH3CH2O-, CH3(CH2)2O-, (CH3)2CHO-, CH3(CH2)3O-, etc .] and that the N-oxide thus obtained, can be reduced quantitatively to the corresponding 2, 6-lutidine derivatives by iron powder and acetic acid or phosphorus tribromide, which were oxidized to 4-alkoxypyridine-2, 6-dicarboxylic acid with potassium permanganate (Scheme 2).

3 or 4-acetamino-pyridine-2, 6-dicarboxylic acid may further be hydrolyzed to corresponding amino-pyridine-2, 6-dicarboxylic acid at pH 6 reflux for 0.5h (Scheme 2).

All products were characterised by NMR, IR and MS5.

## Acknowledgments

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## References and Notes

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5. Compound $\mathbf{D_2}$: $^1$H NMR (90MHz, DMSO-$D_6$): δ 8.41 (s, 2H), 7.95 (d, 2H), 7.02 (d, 2H), 3.72 (s, 3H). IR (KBr): 3479, 2924, 2551, 1714, 1602, 1518, 1447, 1257, 1180, 1025, 793 cm$^{-1}$. m/z (FAB*)*: 274 ($M^+$+1, 42%). Compound $\mathbf{6_a}$: $^1$H NMR (90MHz, $CDCl_3$): δ 7.76 (s, 2H), 4.00 (s, 3H). IR (KBr): 3487, 3247, 3085, 1721, 1602, 1567, 1468, 1377, 1324, 1201, 1046, 899, 765 cm$^{-1}$. m/z (FAB): 198 ($M^+$+1, 32%). Compound **9**: $^1$H NMR (500MHz, DMSO-$D_6$): δ 10.87 (s, 1H), 8.38 (s, 2H), 2.14 (S, 3H). IR (KBr): 3451, 3325, 3135, 3107, 1728, 1686, 1595, 1535, 1397, 1324, 1250, 1032 cm$^{-1}$. m/z (FAB): 224 ($M^+$, 28%).

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