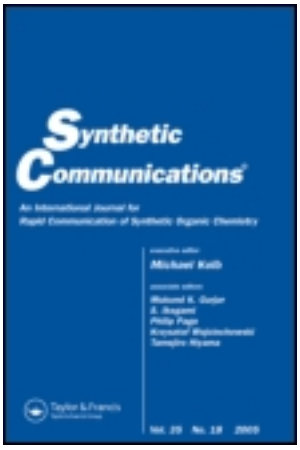

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Controlled Synthesis of 2-Acetyl-6-carbethoxypyridine and 2,6-Diacetylpyridine from 2,6-Dimethylpyridine

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Abstract: The controlled syntheses of mono- and bis-acetylpyridine from the same starting material (2,6-dimethylpyridine) are reported, including the asymmetrical compound 2-acetyl-6-carbethoxypyridine, which has not before been reported. The influences of the amount of catalyst EtONa and the reaction conditions to the final products are also explored. A modification of the reported preparation for the 2,6-dipicolinic acid, 2,6-dicarbethoxypyridine and 2,6-diacetylpyridine with

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higher purity and improved yields is provided here, and the physical and spectral properties of these products are identical to those reported in the literature.

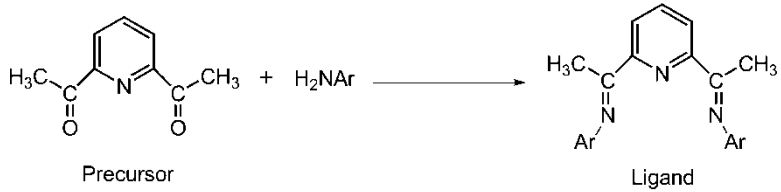
Keywords: Controlled synthesis, EtONa, mono- and bis-acetylpyridine, reaction conditions

INTRODUCTION

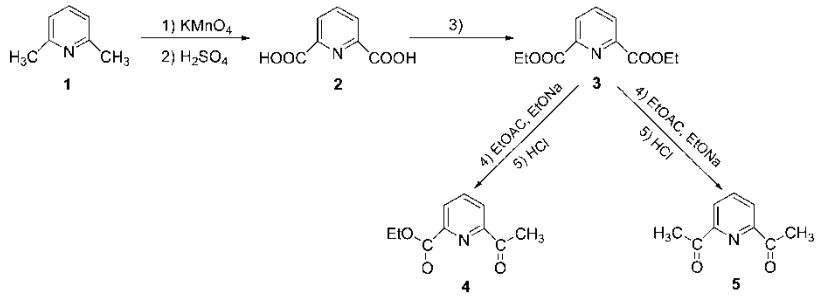
Since late transition-metal catalyst systems containing bis(imino)pyridine ligands have been proven to be significant ethylene polymerization and oligomerization catalysts by the groups of Brookhart[1] and Gibson[2] in 1998, a considerable amount of effort has been dedicated to this field.[3] As a precursor of bis(imino)pyridyl ligand (Scheme 1), 2,6-diacetylpyridine requires an efficient and general synthetic route. Moreover, designing and developing new analogues of 2,6-diacetylpyridine are urgent and significant work in the field of ethylene polymerization catalysis.

RESULTS AND DISCUSSION

During the course of our research, we have designed and synthesized 2-acetyl-6-carbethoxypyridine under the reaction conditions slightly different from that of 2,6-diacetylpyridine. We report here the efficient synthesis methods for 2-acetyl-6-carbethoxypyridine and 2,6-diacetylpyridine starting from relatively inexpensive 2,6-dimethylpyridine (Scheme 2). At the same time, we have explored the optimum amount of the catalyst, EtONa, to form the desired product from which we can synthesize mono- and bis-acetylpyridine. 2,6-Dimethylpyridine (**1**) is commercially available. It is converted to 2,6-dipiclinic acid (**2**) by a modified procedure with better yield than that reported by Singer and McElvain.[4,5] (Singer and McElvain[4] reported a mp of 227–228°C for this compound. The difference may have been due to the presence of traces of moisture and H_2SO_4, which appear to lower the mp markedly.) Esterification of **2** is done according to a method slightly different than that previously reported,[4,6] obtaining 2,6-dicarbethoxypyridine (**3**), which is purified by a simplified method. Compound **3** is dissolved in



Scheme 1.



Scheme 2. 3) EtOH oil-water separator, using H_2SO_4 and benzol to remove water. The reaction conditions to prepare 4 and 5 are slightly different.

freshly distilled EtOAc, and then treated with dry EtONa powder and excess of concentrated HCl to afford the final products 2-acetyl-6-carbethoxypyridine (**4**) or 2,6-diacetylpyridine (**5**). The molar ratio between EtONa and intermediate **3** is a decisive factor.

To ascertain the role of EtONa in the synthesis of 2-acetyl-6-carbethoxypyridine and 2,6-diacetylpyridine, we have designed a series of experiments in which the molar ratio of EtONa to **3** and other reaction conditions are regularly changed (Table 1). The results show that the desired reaction hardly takes place because small traces of EtOH or H_2O exist in EtONa powder (see Table 1, **a**). Thus, EtONa used in the next four experiments has been dried in vacuum at least for 6 h. When molar ratio of reactant **3** to catalyst EtONa is used as described in Ref. 7, products **4** and **5** are both obtained (this is different from the results reported in Ref. 7; see Table 1, **b**). As a solvent that is also one of the reactants, EtOAc is excessive in this reaction. The yield of the reaction has not been significantly improved when

Table 1. Influence of molar ratio between EtONa and **3** to the products and the yields

	Reactants			Products, yield (g, %)	
Run	3 (g, mol)	EtONa (g, mol)	EtOAc (mL)	**4**	**5**
a	11.17 (0.05)	6.20 (0.09)	20	Trace	Trace
b[7]	11.17 (0.05)	6.20 (0.09)	20	2.69 (27.8)	1.48 (18.1)
c	11.17 (0.05)	6.20 (0.09)	40	2.71 (28.0)	1.55 (18.9)
d	11.17 (0.05)	4.08 (0.06)	40	4.35 (45.0)	—
e[8]	11.17 (0.05)	15.64 (0.23)	40	—	4.80 (58.8)

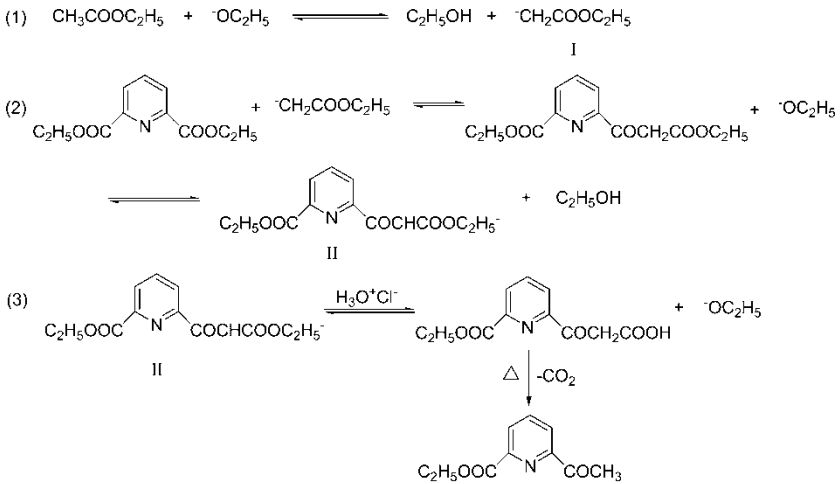
a. Residual humidity and EtOH has not been eliminated completely in this experiment.

b, **e**. Molar ratios among reactants are in accordance with data reported in Refs.[7,8], respectively.

a large excess of EtOAc (twice that in **b**) is used (see Table 1, **c**). Therefore, quantity of EtONa seems to be the decisive factor to the final products and yields. By reducing the molar ratio (EtONa : **3**) to about 1 : 1, only **4** is obtained (see Table 1, **d**). When the molar ratio of EtONa to **3** is increased nearly to 5 : 1, the final separated product is only **5** (see Table 1, **e**). Considering these results, we find that quality and quantity of EtONa in the reaction are key elements for final products and yields. This accords with the conclusion illustrated in Scheme 3. Compound **4** can be obtained when the molar ratio of EtONa to **3** is controlled between 1.2 and 1.5, and **5** can be obtained between 4.5 and 5.0.

Comparing our results of experiment **b** (Table 1) with that of reported in literature,[7] we have found there are some problems in literature.[7]

1. Our experiment shows that the final product reported in literature[7] is not only the 2,6-diacetylpyridine, but the mixture of 2-acetyl-6-carbethoxypyridine in major and 2,6-diacetylpyridine in minor amounts. This mixture has been separated by column chromatography and proved by ^{1}H NMR, MS, IR, and elemental analysis respectively.
2. The melting point (44–46°C) of 2,6-diacetylpyridine reported in this literature[7] is not comparable to other literature[8,9] (mp 79–80°C) and commercial-grade specification[10] (mp 80°C). Through exploration, we have found the melting point reported in literature[7] is an eutectic point of 2-acetyl-6-carbethoxypyridine and 2,6-diacetylpyridine (see Fig. 1). Melting point of 2,6-diacetylpyridine is determined to be 79–80°C after separation from the mixture and it is comparable to the literature[8,9] and commercial-grade specification.[10]



Scheme 3. Mechanism of the reaction to prepare 2-acetyl-6-carbethoxypyridine.

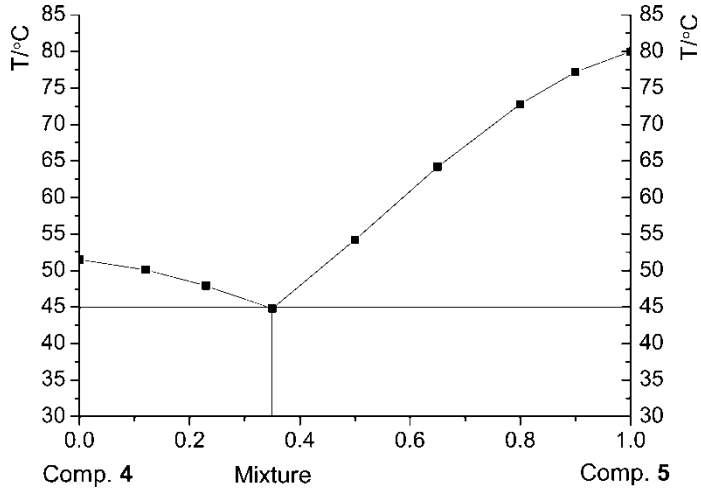


Figure 1. Melting-point composition diagram of binary system comp. **4** and comp. **5**.

We assume the mechanism (see Scheme 3) of the reaction to prepare **4** might be the following: Ethoxide ion abstracts (step 1) a hydrogen ion from the α-carbon of the ethyl acetate to form carbanion I. The powerfully nucleophilic carbanion I attacks (step 2) one of the carbonyl carbon of 2,6-carbethoxypyridine to displace ethoxide ion and yields the keto ester. Then, keto ester reacts with ethoxide ion to form ethyl alcohol and the salt of keto ester, which is essential to the success of the reaction; of the various equilibria involved in the reaction, only this step is favorable to the product we desired. Because step 1 and 2 are equilibrium reactions, it is necessary to use an excess of the EtONa or else to remove the product EtOH from the reaction mixture to shift the equilibrium to the right. Acidic hydrolysis of II (step 3) is promoted by removal of CO_2 produced in reaction through heating, and the final product **4** is afforded. During the experiment, we have detected production of CO_2 using suspension of $Ca(OH)_2$, which also confirms the mechanism.

In summary, we have realized the controlled synthesis of mono- and bis-acetylpyridine from the same starting material 2,6-dimethylpyridine and modified the reported synthesis procedures of **2**, **3**, and **5**. It is noteworthy to mention here that, to the best of our knowledge, the preparation of 2-acetyl-6-carbethoxypyridine (**4**) has not been reported. The frame of this new asymmetrical compound is a straightforward modification of the structure of 2,6-diacetylpyridine, which may lead to a series of new monoiminopyridine ligands, according to our initial research. The transition-metal compounds bearing these ligands as the catalysts for ethylene polymerization would be quite a significant subject to study.

EXPERIMENTAL

Infrared spectra were obtained as KBr pellets on a Perkin-Elmer FTIR 2000 spectrometer. ^{1}H NMR spectra were recorded on a Bruker spectrometer DMS-300 with TMS as the internal standard. EI-Mass spectra were measured on a Kratos AEI MS-50 instrument. Elemental analyses were carried out on a HP-MOD 1106 microanalyzer. Melting points were taken on a XT-4 melting-point apparatus and are uncorrected. 2,6-dimethylpyridine was purchased from Aldrich Chemical Company. Silica gel 60 F_{254} (Merck) was used for TLC. EtOH and EtOAc were dried and purified by the standard purification procedures and used as freshly distilled.

Preparation of 2,6-Dipicolinic Acid (2)

In a 2-L, three-necked flask fitted with a reflux condenser, 16.7 g (0.156 mol) of 2,6-dimethylpyridine (**1**) was added to a solution of potassium permanganate (53.3 g, 0.34 mol) in 750 mL of water. After refluxing for about 1.5 h until the color of potassium permanganate had nearly disappeared, another 53.3-g portion of potassium permanganate was added through one branch of the three-necked flask and washed with 150 mL of water. The heating was continued until the purple color was dissolved again (2–2.5 h). The mixture was cooled to room temperature, and manganese dioxide was filtered and washed with 30 mL of hot water. The filtrate was collected and concentrated to about 200 mL, then filtered to remove the residual manganese dioxide, and acidified with slightly excess of concentrated H_2SO_4 (98%, 18.7 mL). The solution was allowed to stand under room temperature for about 6 h to afford white crystals of dipicolinic acid, which were collected by filtration and dried in vacuum. The filtrate was acidified with H_2SO_4 again and cooled to 0°C; 10% of product can be recovered and thus the yield was improved to 70% (18.24 g). Mp 250–251°C (lit.[4] 64%, mp 227–228°C; lit.[5] mp 250°C).

Preparation of 2,6-Dicarbethoxypyridine (3)

Dipicolinic acid (33.4 g, 0.2 mol) was refluxed with 400 mL of absolute ethanol for a 24-h period using 8 mL of concentrated H_2SO_4 and 20 mL of benzol. The water was removed by an oil–water separator. After excess of ethanol was distilled, 100 mL of water was added and the residual acid was neutralized to pH = 6.5–7.0 with Na_2CO_3 powder. The resulting mixture was abstracted with $CHCl_3$ (5 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and dried in vacuum; white crystals were obtained in good yield (37.02 g, 83%) (lit.[6] 60%) and high purity (mp 41.0–41.5°C) (lit.[6] 41–42°C).

Preparation of 2-Acetyl-6-carbethoxypyridine (4)

Sodium (2.10 g, 0.09 mol) was dissolved in 60 mL of pure and dry ethanol, then excess of ethanol was removed, and the obtained white powder was dried in vacuum for 3 h. 2,6-Dicarbethoxypyridine (11.17 g, 0.05 mol) in 40 mL of freshly distilled EtOAc was added dropwise to the dry EtONa powder with stirring to afford a yellow mixture, which was refluxed for 12 h and allowed to stand overnight. Excess (33 mL) of concentrated HCl was added dropwise with stirring to the resulting mixture and refluxed for a period of 7–8 h to complete the reaction. After water was added to dissolve the NaCl formed in the reaction, the mixture turned to an orange solution (100 mL). The aqueous phase was shaken with $CHCl_3$ (4 × 25 mL). The combined extracts were washed with 5% aqueous Na_2CO_3 and the aqueous phase was extracted by $CHCl_3$ (3 × 10 mL) again. The combined organic phase was dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The obtained mixture was separated by column chromatography (silica-gel, petroleum ether–EtOAc = 4 : 1). First eluted was 2,6-diacetylpyridine (yield: 1.55 g, 18.98%). Second eluted was 2-acetyl-6-carbethoxypyridine (yield: 2.71 g, 28.0%). Mp 50.0–51.5°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, Py-Hm), 8.20 (d, 1H, Py-Hm), 7.99 (t, 1H, Py-Hp), 4.49 (m, 2H, CH_2), 2.81 [s, 3H, O═C(CH_3)], 1.47 [t, 3H, $CH_2(CH_3)$]. IR (KBr) $\nu_{C=O}$ 1725.98 cm^{-1}, 1705.83 cm^{-1}, ν_{C-O-C} 1155.74 cm^{-1}. MS (EI): m/z 193 (M^+). Anal. calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.51; H, 5.76; N, 7.30.

Preparation of 2,6-Diacetylpyridine (5)

The procedure was the same as that of compound **4**. The key difference was the purity, dryness of EtONa, and the molar ratio of EtONa to the compound **3**. Sodium (5.3 g, 0.23 mol) was dissolved in 130 mL of pure and dry ethanol. The obtained EtONa powder was dried in vacuum at least for 6 h to get rid of ethanol completely. 2,6-Dicarbethoxypyridine (11.17 g, 0.05 mol) in 40 mL of freshly distilled EtOAc was added. The final product **5** was purified by column chromatography and recrystallized from ethanol. Yield: 4.8 g, 58.8%; mp 79.0–80.0°C (lit.[8] yield: 61.3%, mp 79°C; lit.[9] mp 78–80°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 2H, Py-Hm), 8.01 (t, 1H, Py-Hp), 2.81 [s, 6H, O═C (CH_3)]. IR (KBr) $\nu_{C=O}$ 1704.83 cm^{-1}. MS (EI): m/z 163(M^+). Anal. calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.24; H, 5.53; N, 8.73.

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