A Facile and Efficient Approach to the Synthesis of 2,6-Diacetylpyridine

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Summary: 2,6-Diacetylpyridine was synthesized *via* esterification by using pyridine-2,6-dicarboxylic acid as precursor and successive Claisen condensation promoted by sodium for the first time. Compared with traditional sodium ethylate promoted Claisen condensation, the yield of 2,6-diacetylpyridine was improved greatly, and the procedures were simpler and convenient.

Introduction

As an important intermediate in organic synthesis, 2,6-diacetylpyridine (DAP) can react with amines to produce large ring ligands, which are widely used in medicine and asymmetric catalysis [1-3]. Moreover, DAP is the indispensable material for the preparation of bis(imino)pyridyl iron complexes [4,5], which are regarded as the third generation highly active catalyst precursors for olefin polymerization after Ziegler-Natta catalysts and metallocene catalysts.

Up to now, two methods have been developed for the synthesis of DAP. DAP can be synthesized *via* Claisen condensation from 2,6-dicarbethoxypyridine (DCP) and ethyl acetate with sodium ethoxide as a base [6], which requires to remove trace of ethanol or water from reaction system, otherwise the presence of ethanol and water will greatly decrease the yield of DAP. Furthermore, sodium ethoxide is obtained from sodium reacting with ethanol, and must be dried entirely before being used. DAP can also be prepared from pyridine-2,6-dicarboxylic acid reacting with methyllithium catalyzed by CuI [7], which needs rigorous experiment technology and expensive methyllithium.

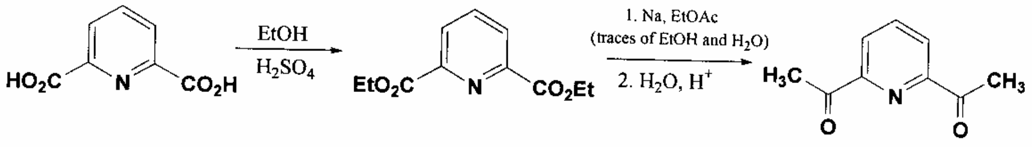
Alkali metals can be used directly in Claisen condensations, which is less concerned [8]. Thus, instead of using sodium ethoxide, we tried alkali metals to prepare the DAP. The process proved to be very simple and convenient. The synthesis route was shown in scheme-1.

Results and discussion

The reactants were not purified before using, and little ethanol and water existed in reaction system inevitably. Thus sodium can react with ethanol to obtain sodium ethoxide, which can extract hydrogen from ethyl acetate to form anion. The ethyl acetate anion can react with DCP by Claisen condensation, and then hydrolyzes to obtain DAP.

The reaction conditions affected the yield of DAP greatly, which is shown in Table-1.

The results show that alkali metal Na and K can be used directly to produce DAP, and Na shows much higher activity than K and C_2H_5ONa. Furthermore, materials and solvent need not be purified and can be used directly.



DCP

DAP

Scheme-1

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Table-1: Effect of Reaction Conditions on the Yield of DAP[a].

Entry	Base	Molar ratio of Na and DCP	Yield (%)
1	Na	5:1	86
2	K	5:1	42
3	C_2H_5ONa	5:1	31
4[b]	C_2H_5ONa	5:1	58
5	Na	1:1	15
6	Na	2:1	40
7	Na	3:1	59
8	Na	4:1	73
9	Na	6:1	84

a. Reaction temperatures were refluxing temperature

b. Toluene was distilled after dehydration by molecular sieve. Ethyl acetate was refluxed for 4h from acetic anhydride and distilled.

The yield of the DAP was also affected by the molar ratio of sodium and DCP (Table 1, entry 1, 5-9). The yield of DAP increased as the ratio of the sodium and DCP rose from 1:1 to 5:1. However, the yield did not increase as the ratio was increased further.

In summary, DAP can be synthesized with good yield by Claisen condensation promoted by sodium. Compared with the traditional route, this approach is simpler and convenient and the yield is much higher.

Experimental

Mps were obtained on X-5 melting point detector and are uncorrected. ^1H NMR spectra were recorded on Bruker Avance 300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. Elemental analyses were performed using a Heraus Carlo Erba 1108 analyser. Pyridine-2,6-dicarboxylic acid (98%, Alfa Aesar company), sodium, toluene (AR) and ethyl acetate (AR) were used without further purification.

Synthesis of DCP

A mixture of pyridine-2,6-dicarboxylic acid (16.7 g, 0.1 mol), ethanol (140 mL), toluene (80 mL) and sulfuric acid (2 mL) was refluxed for 12 h, with azeotropic removal of water using a Dean-stark trap. The mixture was cooled to room temperature, then it was concentrated and Na_2CO_3 was added in 40 ml water to neutralize the solution. The solution was extracted with Et_2O and filtrated after being dried by Na_2SO_4 and then the Et_2O was removed. White solid was obtained. Yield: 20.9 g (93.7 %); M.p. 41-42 °C, *lit.* [9] 42-43 °C. *Anal.* Calcd. for C11H13NO4: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.22; H, 5.82; N, 6.30.

Synthesis of DAP

A solution of DCP (4.46 g, 0.02 mol), sodium (2.3 g, 0.1 mol) and ethyl acetate (50 mL) in toluene (80 mL) was refluxed for 9 h. The mixture was cooled to room temperature, then 50 ml conc. HCl and 40 ml H_2O were added, and the mixture was refluxed again for 5 h. The mixture was neutralized by the gradual addition of solid Na_2CO_3, then extracted with Et_2O (30 mL) three times and dried (Na_2SO_4). After removal of Et_2O, the crude product was purified by chromatography on silica gel (ethyl acetate-petroleum ether 1:5, v/v) to yield DAP as white solid 2.81 g (86 %); M.p.79.0-80.0 °C, *lit.* [6] 79.0 °C. ^{1}HNMR (300 MHz, $CDCl_3$): δ2.77 (s, 6H, O=C-CH_3); δ7.96(t, 1H, H_{Py}); δ8.18(d, 2H, H_{Py}). *Anal.* Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.58; N, 8.53.

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