

A "One Pot" Synthesis of Polysubstituted Pyridines from Metallated Alkylphosphonates, Nitriles and α,β -Unsaturated Ketones.

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Abstract: A simple and efficient synthesis of polysubstituted pyridines is described. The key step is based on the regioselective addition of lithiated β -enaminophosphonates **5** to unsaturated carbonyl compounds **3**. Pyridines **1** can also be obtained in "one pot" reaction from phosphonates **6** when these compounds are metallated followed by addition of nitriles and unsaturated carbonyl compounds.
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Pyridine ring systems represent an important class of compounds¹ not only for their theoretical interest but also because they constitute the skeleton of some alkaloids,² of some antitumor antibiotic³ and because many of these compounds display strong biological activity.²⁻⁴ Moreover, pyridine derivatives have remarkable versatility in synthetic organic chemistry as intermediates in the preparation of natural products⁵ and as ligands⁶ in transition metal complexes preparation recently used in asymmetric synthesis.⁷

A wide range of procedures for the synthesis of pyridines^{8,9} has been reported and, especially in the case of the preparation of multisubstituted pyridines, a convergent approach to the construction of the six membered ring systems¹ could be the [4+2] cycloaddition reaction of 2-azadienes^{10,11} **2**, (Scheme 1). However, general synthetic applications of these cycloadditions encounter limitations to the access of functionalized substitution pattern.¹² An alternative method for synthesizing polysubstituted pyridines could involve the [3+3] pyridine synthesis (Scheme 1) using α,β -unsaturated carbonyls **3** as the 3-carbon component and primary enamines as the 2-carbon component **4**. This strategy has been recently used in an elegant synthesis of pyridines from primary enamino nitriles **4** and carbonyl derivatives¹³ **3**. However, this method requires the presence of an electron-withdrawing group in the β -carbon of the enamine, the cyano group, in order to stabilize the primary enamine group and therefore in the reaction very toxic hydrocyanic acid is produced and eliminated.

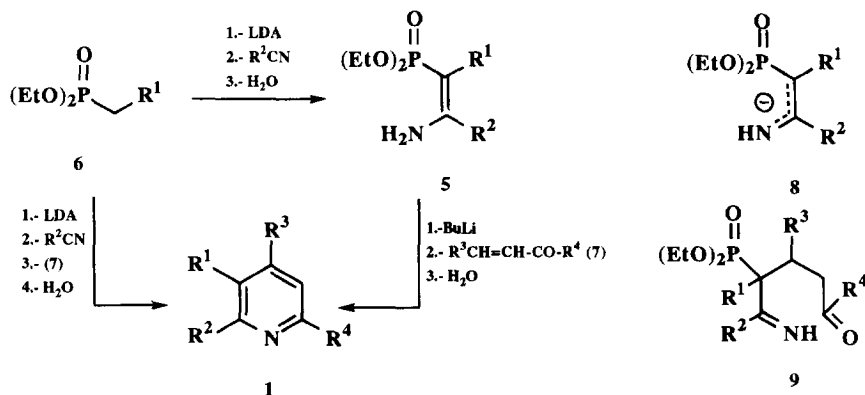


Table 1. Pyridines **1** obtained.

Entry	Compound	R ¹	R ²	R ³	R ⁵	Yield (%)	m.p. (°C)
1	1a	H	<i>p</i> -CH ₃ -C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	90 ^a (77) ^b	124-125
2	1b	H	2-Pyridyl	C ₆ H ₅	C ₆ H ₅	87 ^a (73) ^b	161-162
3	1c	H	2-Furyl	C ₆ H ₅	C ₆ H ₅	81 ^a (70) ^b	94-95
4	1d	H	<i>p</i> -CH ₃ -C ₆ H ₄	CH ₃	C ₆ H ₅	62 ^a (50) ^b	92-93
5	1e	CH ₃	<i>p</i> -CH ₃ -C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	65 ^a (50) ^b	126-127
6	1f	CH ₃	2-Pyridyl	C ₆ H ₅	C ₆ H ₅	60 ^a	91-92
7	1g	C ₆ H ₅	<i>p</i> -CH ₃ -C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	91 ^a (75) ^b	170-171
8	1h	C ₆ H ₅	<i>p</i> -CH ₃ -C ₆ H ₄	CH ₃	C ₆ H ₅	55 ^a	87-88

^a Yield of isolated product **1** based on **5**. ^b Yield of isolated product in "one pot" reaction from **6**.

In conclusion, we describe a new strategy for an easy and efficient method for the regioselective synthesis of polysubstituted pyridines **1** from readily available starting materials and under mild reaction conditions. Polysubstituted pyridines are useful heterocycles not only for their application in organic synthesis⁷ but also for their biological activities²⁻⁴, moreover, the pyridine nucleus is a structural unit appearing in many natural products⁵. Further studies on compounds **5** are now in progress in our laboratory.

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20. Preparation of primary β -enaminophosphonates (**5**, R¹=H) has been previously reported¹⁶. In order to extend the scope of this synthetic methodology, new enamines (**5**, R¹=CH₃, C₆H₅) have been obtained.
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23. Typical procedure for the preparation of pyridine **1a**. A dry flask, 100 ml, two necked, fitted with a dropping funnel, gas inlet, and magnetic stirred, was charged with 5 mmol of BuLi and 25 ml of dried THF at 0°C under N₂ atmosphere, and a solution of enamine (2-diethoxyphosphoryl *p*-tolyl ethenylamine)¹⁶ (1.35 g, 5mmol) in 25 ml of THF was then added. After stirring for 1h. at 0°C, the resulting mixture was slowly warmed up to room temperature (45min.). A solution of Chalcone (1.05g, 5mmol) in 25 ml of THF was slowly added, and the reaction mixture was stirred at room temperature until completion (tlc control), approximately 12h. The mixture was then diluted with 50 ml of water and extracted with CH₂Cl₂. The CH₂Cl₂ layers were washed with water. The organic layers were dried over MgSO₄, and filtered. Evaporation of the solvent followed by flash chromatography (neutral aluminum oxide; eluent, hexane), afforded 1.43g. of compound **1a**, which was recrystallized from hexane.
24. All new compounds reported here gave satisfactory elemental analysis. Spectral data for **1a**: ¹H-NMR (CDCl₃, TMS, 300 MHz) δ 2.35 (s, 3H, CH₃), 7.21-8.14 (m, 16H, arom.) ppm. ¹³C-NMR (CDCl₃, TMS, 75 MHz) δ 21.5 (CH₃), 117.0-157.7 (C arom.) ppm.
25. Spectral data for **1g**: ¹H-NMR (CDCl₃, TMS, 300 MHz) δ 2.34 (s, 3H, CH₃), 2.61 (s, 3H, CH₃), 7.18-7.96 (m, 11H, arom.) ppm. ¹³C-NMR (CDCl₃, TMS, 75 MHz) δ 21.3 (CH₃), 24.8 (CH₃), 115.8-158.7 (C arom.) ppm.