

## Addressing the Unusual Reactivity of 2-Pyridinecarboxaldehyde and 2-Quinolinecarboxaldehyde in Base-catalyzed Aldol Reactions with Acetophenone

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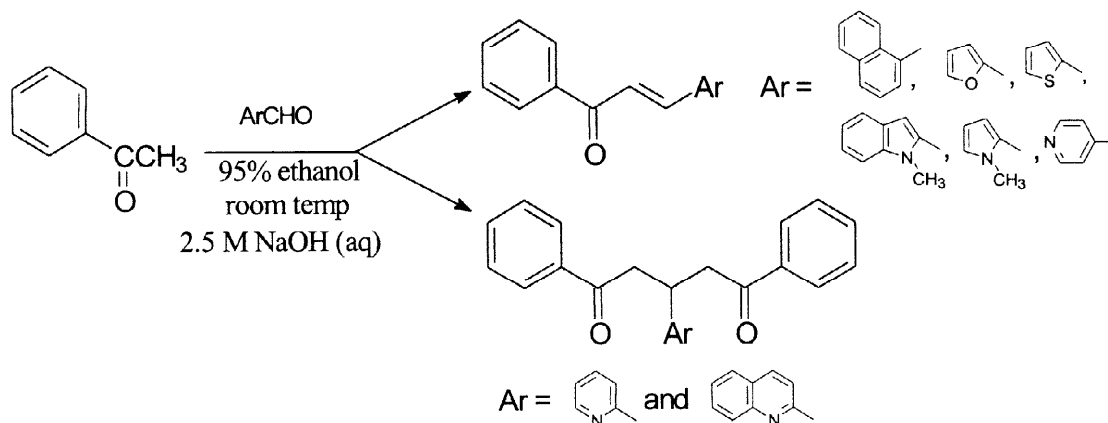
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Received 27 February 1998; revised 13 March 1998; accepted 1 April 1998

**Abstract:** 2-Pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde undergo rapid, tandem aldol-Michael reactions with the lithium, sodium, and potassium enolates of acetophenone at room temperature to give high yields of 3-(2-pyridinyl)-1-phenyl-2-propenone and 3-(2-quinolyl)-1-phenyl-2-propenone, respectively. The aldol condensation product can be obtained in high yield when pyridine is added to the reaction mixture.

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The aldol condensation reaction is arguably one of the most useful reactions for the formation of carbon-carbon bonds.<sup>1</sup> Traditionally, base-catalyzed aldol condensation of acetophenone with aromatic aldehydes yields the *trans*-isomer of the corresponding  $\alpha,\beta$ -unsaturated ketones. The rapid elimination of water from the initially formed aldolate generates a fully conjugated product. While investigating the properties of 4-substituted and heteroaromatic chalcones (1,3-diphenylpropenones), prepared by base-catalyzed condensation of appropriate aromatic carboxaldehydes with acetophenone, we encountered an unanticipated effect on the reactions involving 2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde with acetophenone.



Treatment of an ethanolic solution of acetophenone and one equivalent of 2-pyridinecarboxaldehyde with 10 % aqueous NaOH results in formation of a precipitate. Analysis of the white solid recovered after recrystallization from ethanol revealed that the symmetric diketone, 1,5-

diphenyl-3-(2-pyridinyl)-1,5-pentanedione, had been generated. Indeed, proton NMR analysis clearly demonstrates the diastereotopic environments of the  $\alpha$ -methylene protons of the diketone. An extensive search of the literature revealed that the unusual reactivity of 2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde with acetophenone has previously been noted.<sup>2,3</sup> These early attempts at synthesizing 3-(2-pyridine)- or 3-(2-quinoline)-1-phenyl-2-propenone resulted in oily mixtures of the  $\alpha,\beta$ -unsaturated ketone along with the 1,5-diphenyldiketone addition product and unreacted aldehyde. The investigators concluded that only poor to moderate yields of the desired pyridine or quinoline chalcone could be achieved due to the rapidity with which the  $\alpha,\beta$ -unsaturated ketone undergoes conjugate addition with the enolate of acetophenone. Curiously, no attempt was made to optimize the yield of Michael addition product. Herein we describe methodology which exploits the reactivity of the pyridine ring system and permits selective formation of *either* the aldol condensation product *or* the symmetric Michael adduct, both in high yield.

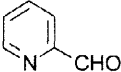
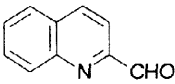
When 2-pyridinecarboxaldehyde is treated with *two* equivalents of either the lithium, sodium, or potassium enolates of acetophenone, the reaction proceeds rapidly at room temperature and high yields (94 %) of 1,5-diphenyl-3-(2-pyridinyl)-1,5-pentanedione are achieved. Similar treatment of 2-quinolinecarboxaldehyde with two equivalents of the sodium enolate of acetophenone results in precipitation of 1,5-diphenyl-3-(2-quinolyl)-1,5-pentanedione from the reaction. The lower yield of the quinoline adduct is in part due to the poor solubility of the larger aldol intermediate in the polar solvent system used (Table 1).

Lewis bases have been shown to catalyze aldol reactions by altering the aggregation state, and thereby the reactivity, of the metal enolate.<sup>4</sup> The product metal aldolate, however, is purported to undergo little or no coordination with ligands such as THF or TMEDA.<sup>5</sup> Recent work by Pospisil *et al.*<sup>6</sup> employing pyridine-lithium pinacolate complexes support the preferential binding of the ligand to the metal enolate relative to the aldolate products. Our results, however, suggest that interaction between the pyridinyl aldolate and metal ion *is* significant for systems containing 2-pyridinyl or 2-quinolyl ring systems. In an effort to impede the reactivity of these aldehydes, pyridine was added to the reaction mixture to compete with the aldolate nitrogen for chelation of the metal ion. Dramatic reductions in the yield of diketone were observed (entries 4 and 6 in Table 1). Notably, a quantitative yield of 3-(2-quinolyl)-1-phenyl-2-propenone is achieved when one equivalent of pyridine is added to the reaction run under equimolar conditions of 2-quinolinecarboxaldehyde and ketone.

A putative explanation for the rapid formation of the diketone involves bidentate coordination of the metal ion by the nitrogen and carbonyl oxygen of the aldolate. The involvement of aggregated intermediates in aldol reactions is well documented.<sup>7</sup> Intramolecular complexation of the metal ion by the aldolate would necessitate that it adopt a conformation where the pyridinyl ring is *gauche*, rather

than anti, to the benzoyl group.  $\beta$ - Elimination from the chelated aldolate would generate the thermodynamically less stable *cis*-alkene which rapidly undergoes Michael addition with a second equivalent of the enolate resulting in nearly quantitative conversion of the carboxaldehyde to the diketone. Alternatively, the condensation product itself, whether the *cis*- or *trans*-isomer, may be coordinating the second equivalent of metal enolate, thereby facilitating its addition to the  $\beta$ -carbon. Attempts to isolate the aldolate are currently under way.

Table 1. Reaction conditions for the formation of the 1,5-diketone.

Entry	Aldehyde	Equiv Aldehyde	Metal cation	Equiv pyridine used	Yield aldol product (%) <sup>a</sup>	Yield Michael adduct (%) <sup>b</sup>
1		0.5	Li	none	trace	93
2		0.5	Na	none	trace	94
3		0.5	K	none	none	98
4		0.5	Na	0.5	75	12
5		0.5	Na	none	15	48 <sup>c</sup>
6		1.0	Na	1.0	100 <sup>b</sup>	none <sup>a</sup>

<sup>a</sup> Determined by GC analysis of filtrate. <sup>b</sup> Isolated yield. <sup>c</sup> GC analysis of the filtrate revealed small amounts of unreacted aldehyde and 2-quinoline chalcone in the product mixture.

*3-(2-Pyridinyl)-1,5-diphenyl-1,5-pentanedione*. To a stirred solution of 1.30 mL (1.34 g, 11.1 mmol) of acetophenone and 0.48 mL (0.54 g, 5.04 mmol) of 2-pyridinecarboxaldehyde dissolved in 5 mL 95% ethanol was added 2 mL 2.5 M NaOH (aq). The solution acquired a golden tint and a white precipitate soon formed. The mixture was poured into cold water, filtered, and the solid rinsed with cold ethanol. The crude product was recrystallized from ethanol to yield 1.54 g (4.68 mmol, 94 %) of quartz-like crystals: mp 121 °C (lit.<sup>2</sup> 119 - 121 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.43 (dd, 2 H, J = 17.10 and 6.00 Hz), 3.64 (dd, 2 H, J = 17.40 and 7.80 Hz), 4.21 (tt, 1 H, J = 7.65 and 6.00 Hz), 7.04 (ddd, 1 H,

$J = 7.20, 4.80,$  and  $1.20$  Hz),  $7.36$  (d, 1 H,  $J = 7.20$  Hz),  $7.40$  (t, 4 H,  $J = 7.80$  Hz),  $7.50$  (tt, 2 H,  $J = 6.60$  and  $1.20$  Hz),  $7.55$  (td, 1 H,  $J = 7.80$  and  $1.80$  Hz),  $7.93$  (d, 4 H,  $J = 7.80$  Hz),  $8.45$  (dd, 1 H,  $J = 4.80$  and  $1.80$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  38.15, 43.53, 121.52, 124.07, 128.06, 128.48, 132.98, 136.33, 136.91, 149.10, 162.89, 198.54.

*3-(2-Quinoline)-1-phenyl-2-propenone*. To a stirred solution of 1.10 mL (1.13 g, 9.43 mmol) of acetophenone and 1.42 g (9.00 mmol) of 2-quinolinecarboxaldehyde in 5 mL 95% ethanol containing 1.0 mL of pyridine was added 2 mL 2.5 M NaOH (aq). The resulting amber solution was stirred at room temperature and within five minutes a precipitate formed. After one hour, mixture was poured into cold water, filtered, and the solid rinsed with water. The crude product was recrystallized from ethanol to yield 2.32 g (8.99 mmol, 100 %) of pale yellow crystals: mp  $113 - 115$  °C (lit.<sup>3</sup>  $116$  °C).

ACKNOWLEDGMENT - Funds to support this work were provided by PRAP and Faculty Research and Development grants administered through Hofstra University. We wish to thank Dr. Francis Picart of the Nuclear Magnetic Resonance facility at the State University of New York at Stony Brook for his assistance in the acquisition of the proton and carbon-13 NMR analyses.

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